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CREATINURIA INDUCED BY METHYL TESTOSTERONE IN THE TREATMENT OF DWARFED BOYS AND GIRLS[1]

LAWSON WILKINS, WALTER FLEISCHMANN AND JOHN E. HOWARD

From the Departments of Pediatrics and Medicine, the Johns Hopkins University, and the Harriet Lane Home, the Johns Hopkins Hospital

Submitted for publication September 19, 1941

Kenyon (1) and his coworkers showed that the intramuscular administration of testosterone propionate to adult males with hypogonadism causes a diminished urinary excretion of nitrogen, potassium, sodium and phosphorus, and an increase of body weight. They found that the excretion of creatine was not increased, and in some cases was even diminished, while the excretion of creatinine was not affected. These findings were in accord with the previous observations of Schittenhelm and Bühler (2) that creatinuria occurs not only in children but also in eunuchs and adult men with sexual underdevelopment, while it is usually absent in normal adult men. These writers and Paschkis and Schwoner (3) observed also that crude preparations of male sex hormones cause a decrease in the creatinuria of hypogonadal males and females.

The experiments of Jailer (4) showed that in monkeys testosterone propionate decreases endogenous creatinuria. Coffman and Koch (5), working on rats, concluded that this androgen promotes the retention of ingested creatine. Pizzolato and Beard (6), however, induced creatinuria in rats through injection of testosterone propionate.

Moricard and Bize (7), Villaret and coworkers (8), and Webster and Hoskins (9) found that sexually underdeveloped boys treated with testosterone propionate showed an acceleration of the rate of growth. A similar growth response was found by Dorff (10) with chorionic gonadotropin. One of us (11) reported that a sexually immature

[1] This work was made possible by a grant from the Commonwealth Fund for the study of endocrine problems in childhood.

dwarf of 23 years treated with methyl testosterone by mouth showed a spurt of growth. Albright and others (12), and Brown and Ross (13) have obtained similar results in dwarfed boys with testosterone propionate. McCullagh and Rossmiller (14) have found that the oral administration of methyl testosterone has androgenic effects similar to testosterone propionate, and also causes increased growth, weight and basal metabolic rate in hypogonadal boys. They did not report the effect of methyl testosterone on the creatine metabolism.

In November, 1940, the writers began a study of the effects of sex hormones on the growth of dwarfs having delayed sexual development. Most of these children had reached an age when the complete absence of any evidence of puberty suggested that they would remain sexually infantile. The patients all had retardation of osseous development ranging from two to seven years. One 22-year-old girl (case 6, Table I) had had clinical and biochemical signs of hypothyroidism. Thyroid therapy over a period of five years caused all signs of thyroid deficiency to disappear but failed to cause any sexual maturation, or acceleration of the rate of growth. Thyroid treatment was continued during the studies with sex hormones. With the exception of this patient, none showed any evidence of hypothyroidism and intensive therapy had failed to cause acceleration of growth. In most of the children treatment with various pituitary growth preparations had been tried without effect.

The studies have included observations on sexual development, growth, bone development, epiphyseal fusion, weight, muscular development, balance studies of nitrogen, urinary excretion of creatine, creatinine and 17-ketosteroids, serum cholesterol, non-protein nitrogen, calcium, phosphorus and phosphatase, and basal metabolic rate. These observations should be of increased value if carried out over long periods of time and will therefore be reported in detail in the future. The present paper is written to call attention to a striking effect of methyl testosterone on the excretion of creatine which was not observed by workers using other androgens.

We have treated with methyl testosterone[2] by mouth five dwarfed, sexually retarded boys ranging in age from 10 years, 8 months to 17

[2] The methyl testosterone used, *Metandren*, was kindly supplied by the Ciba Pharmaceutical Products, Summit, New Jersey.

years. These patients were given 25 mg. methyl testosterone daily. They all showed rapid growth of the genitalia and development of the prostate and secondary male characteristics, although the testes did not increase in size. There was definite acceleration in their rates of growth, and increase in their weight and musculature. Balance studies in which both urine and stools were analyzed showed that a marked retention of nitrogen occurred beginning within one to two days after the onset of treatment. In most instances there was an increase in the basal metabolic rate.

In addition we have treated two dwarfed, sexually underdeveloped girls, aged 14½ years and 22 years, respectively, with a combination of stilbestrol and methyl testosterone. These girls were first treated for about two weeks with 1 mg. stilbestrol daily. Their breasts and labia showed development, and in the younger girl, slight endometrial bleeding occurred. There was no retention of nitrogen or increase of weight. Treatment with a daily oral dose of 25 mg. of methyl testosterone was then begun in addition to the stilbestrol. This caused an immediate retention of nitrogen, followed by gain in weight and acceleration of growth. In a period of observation of five months the older girl has shown no evidence of virilization. Her external genitalia have shown the normal female changes of puberty and pubic hair has developed. The younger girl has shown slight enlargement of the clitoris and her voice has become a little husky so that the dose of methyl testosterone has now been decreased.

The studies on creatine and creatinine excretion were carried out on a metabolism ward during a control period of one to two weeks before the beginning of treatment, and for ten to twenty days after the administration of methyl testosterone was first begun. Treatment with a daily dose of 25 mg. was then continued at home. At the expiration of two to three months, five of the patients were studied again in the hospital, and at the end of five months of continuous treatment a third study was made on two of the patients. In five patients the results of withdrawal of therapy were studied. During the periods of study the patients received "creatine free" diets containing no meat or fish. The diets were constant in each case. The protein intake varied from 1.5 to 2.5 Gm. per Kg. of body weight in the different cases, and the calories from 40 to 65 per Kg. of body

weight. The fluid intake was kept constant in each case and the NaCl intake was approximately constant. Daily specimens of urine were analyzed for creatine and creatinine by the methods of Folin. Studies of the nitrogen balance, serum cholesterol and the basal

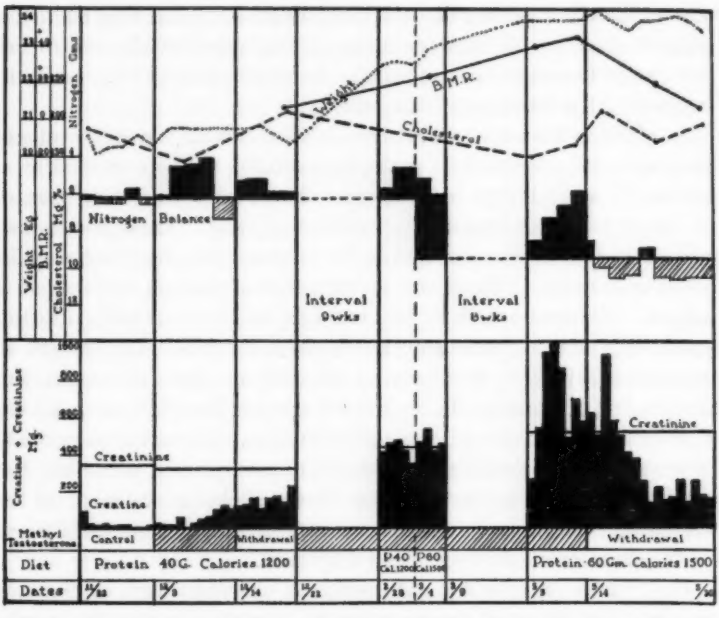

CHART I. EFFECT OF METHYL TESTOSTERONE ON CREATINE AND NITROGEN METABOLISM OF A 16-YEAR-OLD BOY (CASE 2)

In illustrating the nitrogen balance, the base line is drawn to indicate the intake. The figures in the column indicate the total output of nitrogen in Gms. The black columns indicate a positive nitrogen balance, the shaded ones a negative balance.

metabolic rate were carried out at the same time, but will be reported later.

The observations made are illustrated in Chart I. The patient (case 2, Table I) was a 16-year-old boy who had always grown slowly, and now measured 45.4 inches, the height of a 6½-year-old boy, and

had a bone development of 10 years. His features were those of a 9- or 10-year-old boy. The testes were in the scrotum and measured 2.5 x 1.5 cm. The penis was 3 cm. long and 1 cm. in diameter. The prostate could not be felt. No pubic hair was present. The voice was high pitched. There were no clinical or biochemical evidences of thyroid deficiency. He had been under observation since the age of 7 years. In the past five years he had grown 4.4 inches (11.0 cm.) and in the past year 1.0 inch (2.4 cm.). He had been treated on two occasions with intensive courses of pituitary growth preparations and during one course thyroid had been given in addition. No acceleration of growth or development occurred.

During the control period before treatment, the average daily excretion of creatine was 18 mg. or 0.9 mg. per Kg. of body weight. The creatinine output was 352 mg. or 17.6 mg. per Kg. During this period the patient was approximately in nitrogen equilibrium on a 1200 calorie diet, containing 40 Gm. of protein. The third day after methyl testosterone was given there was a decided decrease in the urinary nitrogen which resulted in an average daily retention of 0.9 Gm. nitrogen for the first 11 days of treatment. There was no increase in the excretion of creatine until the 9th day. During the next three days the creatine output averaged 105 mg. or 5.2 mg. per Kg. After 11 days of treatment, methyl testosterone was omitted for a period of 8 days. During this period the excretion of nitrogen increased sharply so that the average daily retention decreased to 0.47 Gm. However, the creatine excretion continued to increase throughout this period, reaching 154 mg. or 9.8 mg. per Kg. at the end. Treatment with a daily dose of 25 mg. of methyl testosterone was then resumed and the patient was allowed to return home. After 9 weeks of continuous treatment at home on an unrestricted diet, he was brought back into the hospital for further study. On the same 1200 calorie creatine-free diet containing 40 Gm. of protein, which he had taken before, there was a nitrogen retention of 0.7 Gm. per day. The creatine excretion had increased to 453 mg. per day, or 19.7 mg. per Kg. The creatinine excretion had increased from 320 mg. to 443 mg. per day. The boy's weight had increased from 20.0 Kg. to 22.3 Kg. and he was very hungry. Accordingly, his diet was increased to 1500 calories, the protein being increased from 40 to 60

Gm. (The increase in the protein intake is shown on the chart by the lowering of the base line.) This resulted in an increase of the nitrogen retention to 3.36 Gm. daily but caused no change in the excretion of creatine or creatinine. After another period of continuous treatment at home with unrestricted diet, the patient again returned to the hospital five months after the beginning of therapy. On the same 1500 calorie diet with 60 Gm. of protein, the nitrogen retention now averaged 1.9 Gm. per day; the creatine excretion averaged 677 mg. or 28.2 mg. per Kg. and the creatinine 535 mg. or 23.3 mg. per Kg. During the five months of treatment he had grown 1.6 inches (4.0 cm.) and had gained 4.0 Kg. weight. The size and strength of his muscles had increased greatly. The penis now measured 6 x 2 cm. The prostate had grown considerably. The scrotum was pigmented and corrugated, but the testes had not changed in size. Considerable coarse dark hair had appeared over the pubis. His voice had become harsh and deep. Treatment with methyl testosterone was now discontinued. Within two days a negative nitrogen balance resulted. The creatine excretion, however, continued at a high level for five days. It then decreased gradually but had not diminished to the low level of the control period on the 18th day after the withdrawal of therapy. The creatinine excretion was not influenced by the withdrawal of treatment. The basal metabolic rate had risen from +7 to +44 per cent (Boothby Sandiford), during treatment, and dropped to +7 per cent fourteen days after methyl testosterone was discontinued. The serum cholesterol showed a moderate decrease during treatment and irregular fluctuations after its withdrawal.

The effects of methyl testosterone on the creatine and creatinine excretion in the seven patients studied are shown in Table I. Before treatment the creatine output ranged between 18 mg. and 65 mg. per day, or 0.9 mg. to 3.5 mg. per Kg. of body weight per day. The average for the group was 40 mg. or 1.7 mg. per Kg. per day. These amounts are smaller than usually excreted by normal, actively growing children. The creatinine excretion ranged between 244 mg. and 621 mg. per day with coefficients of 11.9 to 17.6 mg. per Kg. per day, which were also somewhat lower than normal. After beginning treatment no increase in the creatine excretion was noted until the 5th to

TABLE I

TABLE I

Effect of Methyl Testosterone by Mouth on Excretion of Creatine and Creatinine

CASE	INITIALS H. L. H. NO.	SEX	AGE	HEIGHT	HEIGHT AGE	WEIGHT	BEFORE TREATMENT		DAYS BEFORE RESPONSE	DURING TREATMENT						WITHDRAWAL OF TREATMENT		
										10–20 days		2–3 months		5 months				
							Creatine	Creatinine		Creatine	Creatinine	Creatine	Creatinine	Creatinine	Creatinine	Days	Creatine	Creatinine
			yrs. mos.	*inches*	*years*	*kg.*												
1	N. W. 83008	M	15 9	50.6	8¾	35.0–37.5	27* *0.9*†	532 *15.2*	11	191* *5.5*†	464 *13.3*	408 *10.4*	567 *14.5*	277 *7.1*	683 *17.5*	25–26	69 *1.8*	647 *16.6*
2	F. S. 75271	M	16 0	45.4	6¼	20.0–24.0	18 *0.9*	352 *17.6*	9	105 *5.2*	320 *16.0*	453 *19.7*	443 *19.3*	677 *28.2*	565 *23.5*	16–18	171 *7.1*	510 *21.2*
3	L. B. A-11408	M	10 8	41	4½	18.0–19.2	65 *3.5*	244 *13.6*	5	171 *9.8*	235 *13.4*	568 *29.9*	400 *21.1*			16–18	84 *4.4*	331 *17.4*
4	C. D. A-12222	M	13 6	43.5	5½	15.5–18.2	35 *2.3*	248 *16.0*	7	170 *11.0*	293 *18.9*	184 *10.2*	351 *19.5*			19–21	51 *2.8*	387 *21.0*
5	J. H. 63007	M	17 3	51.6	9¼	23.5–25.0	45 *1.9*	280 *11.9*	8	113 *4.5*	384 *15.4*							
6	A. G. 58209	F	22 1	56.4	11⅓	46.0–42.0	63 *1.4*	621 *13.5*	10	180 *4.1*	594 *13.5*	184 *4.1*	635 *14.1*			22–24	67 *1.6*	661 *15.8*
7	D. T. 74968	F	14 3	48	7⅓	30.0–31.0	28 *0.9*	464 *15.5*	19	194 *6.5*	477 *15.9*							
Average							40 *1.7*	391 *14.8*	9.9	160 *6.6*	395 *15.2*	359 *14.9*	479 *17.7*	477 *17.6*	624 *20.5*	16–26	88 *3.5*	507 *18.4*

* Numerals in ordinary type indicate the average daily excretion of creatine or creatinine in mg.

† Numerals in italics indicate the average daily excretion of creatine or creatinine in mg. per kg. of body weight.

the 19th day in spite of the fact that a decided nitrogen retention occurred within the first day or two. The average time before an increased creatinuria occurred was 9.9 days. The creatine excretion increased gradually and at the end of the first period of study, which was ten to twenty days after the beginning of treatment, it had reached 105 to 194 mg., or 4.1 to 11.0 mg. per Kg. per day. The average was 6.6 mg. per Kg. per day compared to 1.7 mg. per Kg. per day before treatment. During this first stage of treatment changes in the excretion of creatinine were not great nor constant. In some cases there were decreases and in some increases. In no case was the decrease in creatinine excretion sufficient to account for the increased creatine output by a failure of conversion of creatine into creatinine.

After treatment with methyl testosterone had been continued for periods of two to three months, the creatine excretion was restudied in five of the patients. In two of these (cases 4 and 6) the creatinuria was at approximately the same level as at the end of the first ten to twenty days of treatment. In the other three cases (cases 1, 2, 3), the creatine excretion had increased greatly to 408 to 568 mg. per day, or 10.4 to 29.9 mg. per Kg. per day. At the end of five months of continuous treatment the creatine output of one patient had increased to 677 mg. per day, or 28.2 mg. per Kg. per day, while in another patient it had decreased from 408 mg. to 277 mg. After two to five months of treatment the creatinine excretion had increased in every case. In spite of the fact that the patients had all gained weight, the creatinine had also increased in relation to body weight. It was felt that the increased output of creatinine could be accounted for by the absolute increase in the musculature of the patients and the greater proportion of muscular tissue in relation to the total body weight.

In five patients we studied the effect of discontinuing treatment with methyl testosterone after it had been administered continuously for periods of two to five months. Following its omission there was usually a period of six to twelve days during which the creatine output increased to even higher levels than during treatment. After this there was a gradual decrease in the creatinuria. Between the 16th and 26th days the excretion of creatine had decreased to approxi-

mately the levels of the control period as shown in the next to last column of Table I. It should be mentioned that the slow decrease in the creatinuria after withdrawal of therapy is in marked contrast to the effect of withdrawal upon the nitrogen balance. Within one to three days after discontinuing methyl testosterone the nitrogen retention was replaced by a nitrogen equilibrium or even a distinct nitrogen deficit.

DISCUSSION

It was surprising to find that the oral administration of methyl testosterone caused an increased creatinuria whereas the opposite effect has been reported from the intramuscular injection of testosterone propionate. In one hypogonad male treated by methyl testosterone by mouth Tager and Shelton (15) observed a rise in excreted creatine from 225 mg. daily before treatment to 541 mg. and 744 mg. during treatment.

It was first necessary to be certain that the substances being estimated by the Folin method employed were actually creatine and creatinine. This was confirmed by the fact that the 3,5-dinitrobenzoic acid reaction of Langley and Evans (16) gave approximately the same values and that the use of the creatininase enzyme of Dubos and Miller (17) prevented the development of any color reaction both in untreated urine and in urine treated with acid for conversion of creatinine to creatine.

Whether the increased excretion of creatine is a specific effect of methyl testosterone or is caused by other androgens has not been determined. It is possible that the negative results reported by Kenyon *et al.* (1) with testosterone propionate given intramuscularly might be due to the fact that their period of observation was shorter than ours and that their patients were older. We have studied the creatine metabolism in only one patient (case 5) treated with testosterone propionate intramuscularly. Treatment for 21 days with daily injections of testosterone propionate, increasing from 5 mg. to 25 mg., caused marked androgenic effects, but neither nitrogen retention nor creatinuria resulted. In the same patient, three days after beginning methyl testosterone by mouth, nitrogen retention occurred, and on the 8th day increased creatinuria followed. Three of our boys

(cases 3, 4 and 5) and the two girls (cases 6 and 7) were given chorionic gonadotropin (*Follutein*, Squibb), 1000 rat units every other day, for three weeks prior to the study with methyl testosterone. All three boys showed definite androgenic effects and one (case 3) showed nitrogen retention after the 15th day. None had any increase in the creatine excretion. In the two girls there was possibly slight stimulation of sexual development evidenced by questionable beginning development of the breasts. There was no nitrogen retention or increased creatinuria.

Further investigations are being planned to determine the mechanism of the creatinuria brought about by the oral administration of methyl testosterone.

SUMMARY

Five dwarfed, sexually undeveloped boys were treated with methyl testosterone by mouth in doses of 25 mg. daily. Two dwarfed, sexually undeveloped girls were given 1 mg. stilbestrol and 25 mg. methyl testosterone by mouth daily. The administration of methyl testosterone caused retention of nitrogen which occurred within the first one to three days. On an average of ten days after the beginning of treatment, an increase of the output of creatine occurred. This creatinuria continued to increase and was at a high level after two to five months of treatment. On discontinuing methyl testosterone a nitrogen equilibrium or deficit resulted within a few days, while the creatinuria decreased gradually over a period of 16 to 26 days.

We wish to thank Dr. George Harrop of the Squibb Research Institute for furnishing *Follutein*. Dr. Rene Dubos very kindly prepared the enzyme, creatininase, which was used.

We are indebted to Colleen Cox Hambleton of the Dietary Department for the calculation of diets, and to Edward Smetana for technical assistance in the chemical determinations.

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THE ACCURACY OF CLINICAL MEASUREMENTS OF ARTERIAL BLOOD PRESSURE[1, 2]

With a Note on the Auscultatory Gap

CHARLES RAGAN and JAMES BORDLEY, III

From the Department of Medicine, The Johns Hopkins University School of Medicine

Submitted for publication October 22, 1941

When the arterial blood pressure is determined by the auscultatory method, a pneumatic cuff 20 cm. wide will frequently yield lower readings for both systolic and diastolic pressures than those obtained with the standard 13 cm. cuff. The difference is quite significant in some subjects, especially those with large arms. For example, in an obese woman, examined before the present investigation was undertaken, the blood pressure determined with the standard cuff was 165/105, while with the 20 cm. cuff, it was only 104/72. The information gained in the study of this case and of other similar cases led to the tentative conclusion that the standard 13 cm. blood pressure cuff is not wide enough for accurate determinations of arterial pressure in subjects with large arms. The observations here to be reported substantiate this view but at the same time it has been found that the wider blood pressure cuff frequently yields falsely low readings even in obese subjects.

The 13 cm. cuff, now almost universally employed for clinical measurements of blood pressure, was introduced as a result of the investigations of von Recklinghausen in 1901 (6) after it had been demonstrated by indirect methods that the narrower Riva-Rocci cuff (approximately 4.5 cm. in width) gave falsely high readings for systolic pressure as determined by the palpatory method. At that time no method was available for measuring the intra-arterial pressure in

[1] Supported by a grant from the Commonwealth Fund for the study of Essential Hypertension.

[2] Presented in part at a meeting of the Association of American Physicians in May, 1941. (See *Transactions of Association of American Physicians*, **56**: 1941.)

man. Hence, evaluation of the absolute accuracy of the determinations made with the 13 cm. cuff had to await technical advances (for a review of the earlier efforts in this field see von Bonsdorff's monograph (3)).

In 1931, Wolf and von Bonsdorff (8) made use of an optical manometer for recording intra-arterial pressure through a hypodermic needle, in unanesthetized human subjects. They compared the results obtained by this method with the systolic and diastolic pressures determined by the auscultatory (Korotkov) method. Since their studies are the most comprehensive that have been carried out on adult subjects, a summary of their results, as presented in von Bonsdorff's monograph (3), is given in Table I. Twenty-five comparisons were made. In less than half the cases did the auscultatory systolic and diastolic pressure readings come within 5 mm. Hg of the corresponding intra-arterial pressure levels; and in some instances the auscultatory readings were more than 20 mm. Hg either above or below the intra-arterial. Nevertheless, these observations have been interpreted as indicating that the auscultatory method gives a reasonably accurate estimate of intra-arterial pressure. The authors give no information which enables one to judge whether variations in arm circumference might account for some of the discrepancies shown in Table I.

Hamilton and his associates in 1934 (4) introduced an improved optical manometer which was particularly well adapted for recording human intra-arterial pressure. Pressures recorded in adult subjects with this instrument were reported (5) to agree reasonably well with arterial pressures determined by the usual auscultatory method (using, presumably, the standard 13 cm. cuff). The values obtained by the auscultatory method were found to be on the average 3–4 mm. Hg too low for systolic pressure and 9 mm. Hg too high for diastolic pressure. In this report which was of a preliminary character, no mention was made of the sizes of the subject's arms. Subsequently, in studies of newborn infants (9), and of older children (7), Hamilton and his associates made a number of observations showing that the relation between size of arm and size of blood pressure cuff has a very great influence upon the accuracy of indirect measurements of blood pressure. They found that in general the smaller the arm, the narrower the cuff must be; that in new-born infants cuffs wider than 2.5

cm. give falsely low indirect measurements. In relation to the present investigation it may be pointed out that the most uniform correlations were obtained in infants and younger children in whom the contour of the pulse waves was regularly of a full, "central" type.

TABLE I

Summary of results reported by von Bonsdorff in comparing intra-arterial and auscultatory (Korotkov) measurements of arterial pressure (5)

Systolic pressures		
Value obtained by Korotkov method too high	more than 20 mm. Hg—1 case	7 cases
	20–10 mm. Hg—0	
	10– 5 mm. Hg—6 cases	
	less than 5 mm. Hg—5 cases	
No difference between two methods	2 cases	9 cases
Value obtained by Korotkov method too low	less than 5 mm. Hg—2 cases	9 cases
	5–10 mm. Hg—6 cases	
	10–20 mm. Hg—2 cases	
	more than 20 mm. Hg—1 case	
Diastolic pressures		
Value obtained by Korotkov method too high	more than 20 mm. Hg—1 case	8 cases
	20–10 mm. Hg—5 cases	
	10– 5 mm. Hg—2 cases	
	less than 5 mm. Hg—5 cases	
No difference between two methods	1 case	11 cases
Value obtained by Korotkov method too low	less than 5 mm. Hg—5 cases	6 cases
	5–10 mm. Hg—5 cases	
	10–20 mm. Hg—1 case	
	more than 20 mm. Hg—0	

One criticism of all of the earlier work is that the intra-arterial and auscultatory arterial pressures were not determined simultaneously. The intra-arterial pressure may fluctuate considerably within the span of a few seconds (Figure 1) and it is, therefore, important to know the precise point on the intra-arterial pressure tracing at which the auscultatory readings of both systolic and diastolic pressure were made.

Thus the invariable use of a standard cuff, 13 cm. in width, for determining arterial blood pressure in arms of various sizes rests on tenuous grounds. Until the introduction of the modern hypodermic manometer, measurements of intra-arterial pressure in man were not feasible on any comprehensive scale. Since 1931, the work of Wolf and von Bonsdorff and of Hamilton and his associates has shown that in a fair proportion of adult subjects the standard cuff affords reasonably accurate measurements, but that in children the width of the cuff should be regulated in accordance with the size of the arm. It seems quite clearly established that when applied to small arms the 13 cm. cuff yields measurements by the auscultatory method

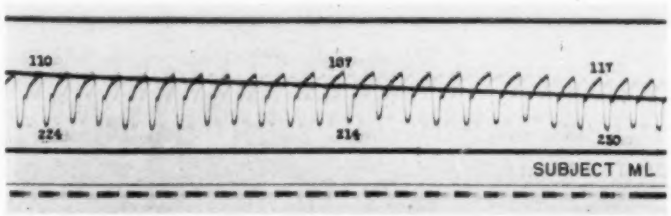

FIG. 1. PHOTOGRAPHIC RECORD OF INTRA-ARTERIAL PRESSURE

Record showing fluctuations which may occur in intra-arterial pressure during a short period (22 seconds). Intra-arterial pressure tracing is inverted, with its base line at the top of the record. Figures refer to systolic and diastolic pressure in mm. Hg. Time in seconds, at bottom of record. (The diagonal line may be disregarded.)

which are too low, but there is no comparable information concerning the suitability of this cuff for arms which are unusually large.

METHODS

The subjects were all adults and were obtained from the medical and surgical wards of the hospital, from the Syphilis Clinic, and from the Hypertension Clinic. Other than the subjects with syphilis who had aortic insufficiency, and some of those with hypertension who had cardiac enlargement, no subjects were studied who had abnormalities of the heart or of the peripheral circulation.

The subjects came to the laboratory and an outline of the procedure was explained to them in an effort to obtain their cooperation. They were placed flat in bed and were allowed to rest for 15-20 minutes. The circumference of the arms was measured with a steel tape at a point half way between the acromion

and olecranon. (The circumference of the right arm only is recorded in the tables and charts.) The two arms were supported on sandbags with both antecubital fossae on the same horizontal plane. The blood pressure was measured in the two arms simultaneously by two examiners by the usual auscultatory method, using standard 13 cm. cuffs and mercury manometers. If the pressures in the two arms obtained on the same pulse beat by the two examiners did not agree at both the systolic and diastolic levels within 2 mm. Hg the experiment was carried no further. After it had been determined that the pressure was the same in the two arms, a 20 cm. cuff was substituted for one of the 13 cm. cuffs and simultaneous pressure determinations were again made.

The patient was then wheeled in bed across the hall to the room where the Hamilton manometer (copper-beryllium membrane) was installed. The lighting system was arranged for use with front-surface plane mirrors which were optically flat. The lead tubing connecting the capsule with the needle was 115 cm. long. The frequency of the membrane was determined before each experiment. In all experiments the frequency exceeded 150 c.p.s.; it was usually between 180 and 220 c.p.s. When not in use the manometer and system were filled with 70 per cent ethyl alcohol. This was replaced with freshly boiled 6 per cent sodium citrate before an experiment. Sterile 20-gauge needles fitted to the lead tubing by a Luer lock were used throughout. The intra-arterial pressure was obtained by inserting the needle through a novocaine bleb in the skin, into the left brachial artery in the antecubital fossa.

Auscultatory arterial pressure measurements were obtained in the right arm.[3] A carbon microphone was placed over the antecubital fossa at the point of maximum arterial pulsation. The Korotkov sounds, picked up by this microphone, were amplified by a vacuum tube set and were passed through a filter (low pass 150 c.p.s.) to two outlets. One outlet was connected to a set of headphones which enabled an observer to hear the sounds. When the observer heard the sounds denoting systolic and diastolic pressure, a button connected to an interruptor was pressed and the signal was recorded on the film. The other outlet was connected to a 1½ inch magnetic loud speaker from which the cone had been cut. A small mirror was attached to the drive-pin or stylus of the loudspeaker for recording its oscillations on the moving photographic paper. This crude stethophone was not adequately dampened and probably gave little indication of the true quality of the sounds. However, it could readily be determined by listening at the earphones that the extent of the deflection of the mirror varied roughly with the intensity of the sounds.

[3] In all instances except one, the intra-arterial pressure was determined only in the left arm. In this one exception, the intra-arterial pressure was first measured in the left arm and compared with simultaneous auscultatory measurements in the right. Then auscultatory measurements were made in the left arm and compared with simultaneous intra-arterial measurements in the right. The pressure differences were the same in the two experiments.

A standard cuff with a pneumatic bag 13 cm. in width and 23 cm. in length was placed about the right arm proximal to the microphone. Throughout the study, the "E-Z On Cuff" (Taylor Instrument Co.) was used. In no instance was the arm so large that the cuff did not fit properly. Excessively obese subjects were avoided.

The pneumatic bag of the cuff was connected by stiff-walled rubber tubing to (a) a calibrated aneroid manometer which was used by the observer in making his readings;[4] (b) a series of pressure bottles by which known pressures could be transmitted rapidly to the cuff; (c) a rubber membrane capsule with a mirror attached for recording pressure changes on the photographic paper. Thus the pressure in the cuff and the sounds picked up by the microphone as the pressure fell could be recorded graphically, simultaneously with the intra-arterial pressure in the opposite arm. The rate of fall of pressure in the pneumatic cuff was not the same in all experiments: it varied from 2.7 to 10.0 mm. Hg per second, with a mean of 5.04 mm. Hg per second. In 80 per cent of the experiments the rate of fall of pressure came within ±2 mm. Hg of the mean.

The Hamilton manometer was calibrated with a mercury manometer after each series of readings. Preliminary tests disclosed that known pressures set up in the Hamilton manometer could be read on the photographic strip with an accuracy of ±3 mm. Hg. The manometer connected to the pneumatic bag of the cuff was also calibrated after each experiment.

One to five graphic records were made on each subject (Table II). In no case were more than three records made on the same day.

RESULTS

Two representative records are shown in Figure 2. One hundred and thirty-eight records of this type were made in 51 adult subjects. The results of these experiments are shown in Table II which also includes the figures obtained in the preliminary blood pressure measurements made with the standard 13 cm. cuff on one arm and a 20 cm. cuff on the opposite arm.

The correlation between the graphic auscultatory measurements and the intra-arterial measurements of *systolic pressure* is shown in Figure 3. If there were perfect agreement between the measurements

[4] The observer recorded his auscultatory readings as one would record them clinically, simply by writing the figures on a slip of paper. These are the figures which have been entered in column 4, Table II. Although the points at which the observer's readings were made were signalled on the photographic records there was necessarily some delay between the observer's recognition of the auscultatory phenomena and his pressing the signal button. The observer's auscultatory readings were therefore not calculated from the graphic records.

TABLE II

Summary of arterial pressure measurements in all subjects

The second and third columns show the results obtained in preliminary measurements in which the pressure determined in the right arm with a large cuff was compared with that determined simultaneously in the left arm with a standard cuff. The first set of measurements recorded (for each subject) in the fourth, fifth and sixth columns was made some 5 to 10 minutes later. The graphs in this paper were constructed from the data recorded in the fifth, sixth and seventh columns. Pressures in millimeters of mercury. Circumference of right arm in centimeters.

SUBJECT, SEX, AGE	PRELIMINARY AUSCULTATORY MEASUREMENTS		OBSERVER'S AUSCULTATORY MEASUREMENTS	GRAPHIC AUSCULTATORY MEASUREMENTS	INTRA-ARTERIAL PRESSURE	ARM CIRCUMFERENCE
	20 cm. cuff	13 cm. cuff				
A. Subjects with normal or low arterial pressure						
R. W., M, 32	98/50	104/70	105/50 104/58	106/51 99/52	104/57 103/57	24.5
R. G., M, 19	110/50	124/64	125/58 126/68	126/59 123/67	127/59 119/68	25.0
L. C., M, 19	115/40	120/44	128/42 126/40	125/47 124/41	134/54 129/52	25.1
J. H., M, 19	114/34	132/60	132/55 126/54 132/58	133/55 130/56 130/50	135/62 133/61 131/59	26.9
D. B., F, 30	108/76	118/80	124/85	125/83	129/63	28.0
S. B., M, 19	115/55	120/70	126/72 126/68	125/73 122/67	130/67 128/66	25.5
E. S., M, 19	104/46	122/70	128/72 128/62 128/65	128/75 126/71 124/74	131/74 129/70 130/69	24.6
J. W., M, 29	108/48	124/64	126/62 122/62 128/60	134/70 132/73 130/68	132/65 132/65 126/62	28.6
H. L., M, 55	112/64	122/68	122/70 114/70 114/70 114/75	126/71 114/69 114/65 114/72	137/61 130/60 130/60 128/62	25.8

TABLE II—*Continued*

SUBJECT, SEX, AGE	PRELIMINARY AUSCULTATORY MEASUREMENTS		OBSERVER'S AUSCULTATORY MEASUREMENTS	GRAPHIC AUSCULTATORY MEASUREMENTS	INTRA-ARTERIAL PRESSURE	ARM CIRCUMFERENCE
	20 cm. cuff	13 cm. cuff				
A. Subjects with normal or low arterial pressure—*Continued*						
J. L., M, 51	74/38	78/44	74/44	78/40	74/33	23.0
			72/46	75/47	70/37	
			70/48	76/47	71/37	
J. L., M, 27	134/50	146/56	145/65	151/63	131/66	32.2
			138/66	145/68	123/66	
A. W., M, 32	108/44	118/68	118/54	120/50	111/56	27.0
			116/60	114/57	100/58	
			116/58	107/51	97/56	
P. P., M, 25	125/52	134/68	134/86	133/84	129/72	32.7
			135/80	131/84	129/67	
			134/80	125/82	123/65	
J. L., M, 30	108/60	120/72	124/80	130/88	108/58	42.5
			120/76	127/78	107/60	
			118/76	123/78	105/54	
A. G., M, 44	106/50	112/66	114/62	112/53	121/51	28.0
			120/68	115/62	124/56	
			112/64	112/59	115/54	
			120/68	117/70	125/56	
J. M., M, 36	100/55	106/62	102/62	105/65	104/51	28.2
			104/60	102/60	101/50	
			102/64	102/66	101/53	
			100/60	102/65	100/50	
E. V., M, 21	90/42	*100/62	98/66	103/64	99/53	26.4
			102/62	102/60	95/52	
			104/64	103/61	97/54	
			108/64	108/60	102/54	
J. H., M, 23	90/45	* 94/70	96/64	96/62	99/58	24.0
			92/62	89/56	94/55	
			92/60	92/48	99/54	
M. P., M, 35			120/72	117/73	118/61	27.3
			120/80	118/81	116/66	
			116/78	118/78	116/64	

TABLE II—*Continued*

SUBJECT, SEX, AGE	PRELIMINARY AUSCULTATORY MEASUREMENTS		OBSERVER'S AUSCULTATORY MEASUREMENTS	GRAPHIC AUSCULTATORY MEASUREMENTS	INTRA-ARTERIAL PRESSURE	ARM CIRCUMFERENCE
	20 cm. cuff	13 cm. cuff				
A. Subjects with normal or low arterial pressure—*Continued*						
H. S., F, 43	148/84	156/92	168/110 158/110	168/97 163/103	121/71 128/85	36.4
D. S., F, 19			102/75 106/80	100/75 104/77	101/63 105/63	28.4
S. P., F, 54	106/70	120/74	130/86 128/86 118/80	125/86 124/81 116/83	120/67 117/63 112/61	33.5
S. T., F, 29	110/56	120/68	126/68	123/71	109/56	27.0
E. E., M, 39	100/60	98/66	112/76	105/69	113/61	27.5
A. J., M, 39	118/64	132/72	126/72	129/70	137/63	29.5
M. W., F, 34	106/70	130/96	125/86 132/92	126/87 132/93	135/87 136/92	29.0
M. W., M, 27	130/84	136/90	136/94 136/96 136/98	133/97 137/92 137/98	139/77 139/81 136/80	27.5
D. P., M, 33	122/68	132/76	156/80 142/84	148/71 132/73	148/66 127/69	28.6
Mean			119/70	119/69	117/61	
B. Subjects with arterial hypertension						
C. W., M, 32	146/94	190/125	182/120 185/120	185/116 184/115	189/104 182/108	34.4
R. L., M, 40	228/142	250/155	240/148 248/150	240/144 250/150	256/130 259/141	27.6
I. C., M, 59	166/95	170/98	178/106 170/108	175/103 168/104	192/94 187/99	23.8
E. S., F, 30	180/113	188/118	220/124 218/132	216/118 213/127	212/104 216/115	25.8
L. O., F, 35	146/92	156/108	160/110 170/120	165/111 170/112	180/100 173/105	24.5
H. B., F, 31	138/104	148/110	158/112 164/116	158/108 158/109	170/102 168/105	24.0

TABLE II—*Continued*

SUBJECT, SEX, AGE	PRELIMINARY AUSCULTATORY MEASUREMENTS		OBSERVER'S AUSCULTATORY MEASUREMENTS	GRAPHIC AUSCULTATORY MEASUREMENTS	INTRA-ARTERIAL PRESSURE	ARM CIRCUMFERENCE
	20 cm. cuff	13 cm. cuff				
B. Subjects with arterial hypertension—*Continued*						
J. L., M, 38	172/106	188/122	196/122 196/126 196/126	197/121 198/122 193/126	204/116 196/109 200/116	26.5
M. H., F, 37	206/102	244/118	240/122 244/125 240/118	237/117 243/117 235/117	258/116 260/117 258/114	26.2
M. L., F, 40	176/94	212/118	212/114 202/120 196/114	212/105 200/112 197/108	215/99 200/107 199/100	32.0
L. S., F, 41	198/116	256/148	264/150	263/152 277/150 269/147	266/130 277/125 273/125	40.5
I. J., F, 31	116/60	146/86	148/88 140/90 142/88 138/84	150/88 147/93 145/90 140/98	150/77 145/85 146/83 141/89	36.3
F. C., F, 52	158/94	186/114	210/? 194/115	209/104 197/110	174/82 172/83	41.0
Mean*			194/117	194/114	200/105	
C. Subjects with syphilitic aortitis and aortic insufficiency						
W. A., M, 40	164/74	170/80	196/88 172/76 172/80 174/80 174/84	196/80 168/75 170/77 174/77 172/84	227/86 200/75 206/79 200/79 198/79	24.5
H. J., M, 57	226/90	232/102	238/105 238/98 238/100	238/101 236/97 238/94	233/92 230/92 235/85	26.0
G. P., M, 31	162/28	162/32	165/0 168/0 178/0	166/19–0 173/20–0 173/20–0	162/48 161/50 162/52	30.5
S. W., M, 27	120/?	130/44	125/18 125/18 128/30	118/19 117/21 120/22	112/45 108/47 120/45	29.6

TABLE II—*Concluded*

SUBJECT, SEX, AGE	PRELIMINARY AUSCULTATORY MEASUREMENTS		OBSERVER'S AUSCULTATORY MEASUREMENTS	GRAPHIC AUSCULTATORY MEASUREMENTS	INTRA-ARTERIAL PRESSURE	ARM CIRCUMFERENCE
	20 cm. cuff	13 cm. cuff				
C. Subjects with syphilitic aortitis and aortic insufficiency—*Continued*						
M. B., M, 51	178/48	186/62	186/60	181/63	191/63	27.3
			184/60	181/68	191/65	
			176/62	176/62	186/68	
			176/62	178/59	185/63	
B. S., F, 54	146/42	146/50	166/56	167/62	165/56	32.0
			158/54	160/59	157/54	
G. M., M, 52	192/72	200/80	186/76	192/79	170/61	30.6
			188/80	186/79	170/62	
			192/78	191/78	176/61	
			186/80	186/76	179/65	
W. P., M, 59	158/68	166/74	164/76	154/78	174/67	24.8
			166/76	161/79	182/73	
			165/70	155/78	172/73	
H. H., M, 44	176/66	178/78	162/58	163/64	174/64	28.0
			162/60	155/62	170/64	
			162/62	155/59	170/64	
			162/62	156/58	172/64	
M. P., F, 55	216/104	240/120	224/110	226/114	218/98	32.2
			226/112	222/107	214/99	
			216/118	216/115	207/104	
F. S., M, 38	96/20	108/38	100/30	98/21	106/32	22.0
			102/30	98/24	106/33	
			106/30	99/14	111/32	
Mean†			173/69	171/68	177/67	
Mean (All cases)*, †			149/79	148/78	150/72	

* In calculating the mean pressures in this group, the second and third series of measurements on subject L. S., and the first series of measurements on subject F. C. were omitted because of incomplete data.

† In calculating the mean pressures in this group the measurements on subject G. P. were omitted.

Note: The occasional discrepancy of as much as 10 mm. Hg between the observer's auscultatory and the graphic auscultatory determinations requires some explanation. Under the conditions of the experiments the observer could not reinflate the cuff to confirm his interpretations as is frequently necessary in clinical work, particularly when the first Korotkov sounds are faint or when the fading of the sounds at the diastolic level is gradual. The observer's readings of diastolic pressure were especially subject to error for in many instances the observer had to wait until he was convinced that the sounds were fading and then try to recollect the pressure level at which the fading had begun. The observer's auscultatory measurements were, therefore, considered to be only approximately accurate.

made by the two methods, all of the points in the graph would fall along the diagonal line. Obviously the correlation is not perfect even when one excludes the readings obtained in cases of aortic insufficiency (open circles).

When the deviation of the auscultatory systolic pressure reading from the intra-arterial systolic pressure is plotted in relation to the size of the arm (Figure 4), a definite trend becomes apparent: with small arms the auscultatory measurements tend to be too low, while with large arms they tend to be too high. However, in some subjects with small arms and in other subjects with large arms the two methods give readings which agree almost perfectly. There must, therefore, be some factor or factors, in addition to the circumference of the arm, which affects the correlation.

In reexamining the records of these experiments, one probably significant factor was noted: in arms of average size when there was a relatively full pulse (J. M., Figure 5) the auscultatory readings agreed very closely with the intra-arterial readings. However, when the pulse was of an empty, peaked type, the auscultatory readings tended to be too low (W. A., Figure 5). A possible explanation of this is that the peaked pulse wave is not well enough sustained to force its way through the compressed artery until the pressure in the occluding cuff has fallen to well below the true systolic level. This effect has also been noted by Bazett and Laplace (1), Hamilton, Woodbury and Harper (5) and others.

In Figure 6 an attempt has been made to show how the contour of the pulse wave appeared to affect the deviation of the auscultatory systolic readings at various arm circumferences. Not all of the pulse contours have been placed on the graph, but a fair sample, including the extreme deviations, is shown. When the arm is small and the pulse peaked, the auscultatory readings are too low. When the arm is large and the pulse full, the auscultatory readings are too high. Looking along the line which indicates good agreement, it may be noted that at one end of the line (small arms) a full pulse gives agreement, while at the other end (large arms) an empty pulse gives agreement. A few exceptions to this generalization may also be noted in the graph.

It occurred to us that some of the disagreements between intra-

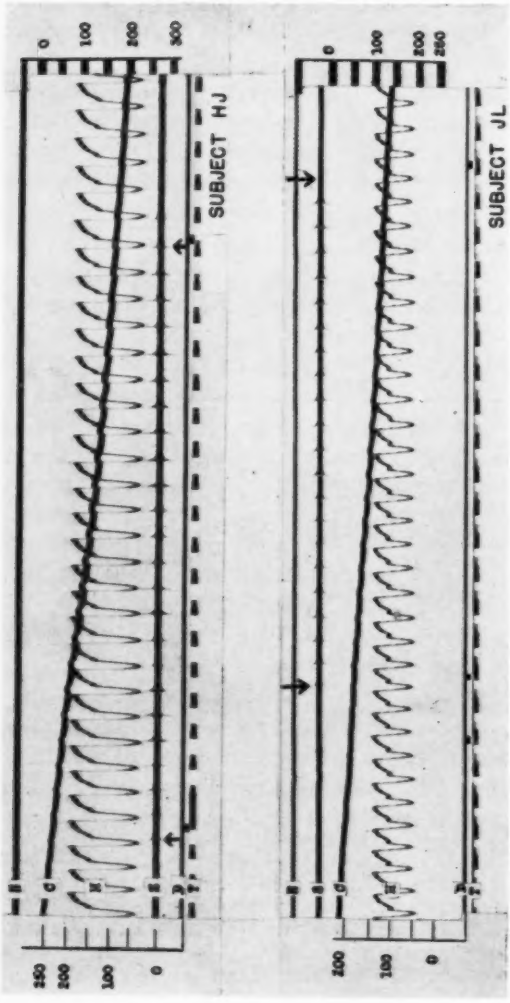

FIG. 2. (Legend on opposite page.)

arterial and auscultatory systolic pressures might be due to the fact that the first pulse wave coming through beneath the cuff did not produce an audible or recordable Korotkov sound. Experiments were, therefore, carried out in a manner similar to the ones outlined above with one additional feature: a cuff of standard width was placed about the left arm proximal to the needle of the Hamilton manometer. The pneumatic bag of this cuff was connected in parallel with the bag of the opposite cuff. Since the two bags were joined through relatively large tubing, and since both were connected in identical fashion with the same pressure bottles and the same recording capsule, a single tracing served to record the pressure changes which were occurring simultaneously in the two cuffs. Figure 7 shows the type of information obtained with this modified set-up in two experiments carried out consecutively on a single subject. Eight such records

FIG. 2. PHOTOGRAPHIC RECORDS OF ARTERIAL PRESSURE IN TWO SUBJECTS

The intra-arterial pressure tracing (H) is inverted with the base line (B) of the Hamilton manometer at the top of each record (calibration in mm. Hg on the right). The line sloping downward from left to right (C) records the pressure in the pneumatic cuff encircling the opposite arm (calibration in mm. Hg on the left). The Korotkov sounds, picked up below the cuff, are shown in the stethophone tracing (S). An observer listening in with earphones pressed the interruptor signal (D) to indicate the points at which he read systolic and diastolic pressures on a standard clinical manometer connected with the cuff. In the case of Subject J. L., the observer at first mistook an extraneous sound for the first Korotkov sound, and pressed the signal prematurely. He corrected his mistake when the first true Korotkov sound was heard.

The arrows point to the first recorded Korotkov sound, and to the first abrupt fade in the sounds. The pressure in the pneumatic cuff was measured at these points to determine the graphic auscultatory systolic and diastolic pressures, respectively. The intra-arterial systolic and diastolic pressures, respectively, were measured at the corresponding points on the intra-arterial pressure tracing. The observer's auscultatory readings were not derived from the graphic records: but were simply written on a slip of paper.

In the case of Subject H. J. the following readings were obtained (in mm. Hg): *systolic pressure* (a) intra-arterial 233, (b) graphic auscultatory 238, (c) observer's auscultatory 238; *diastolic pressure* (a) intra-arterial 92, (b) graphic auscultatory 101, (c) observer's auscultatory 105. Subject J. L.: *systolic pressure* (a) intra-arterial 196, (b) graphic auscultatory 198, (c) observer's auscultatory 196; *diastolic pressure* (a) intra-arterial 109, (b) graphic auscultatory 122, (c) observer's auscultatory 126.

have been made on four subjects. In six of the records (3 subjects), regardless of whether the intra-arterial and auscultatory readings agreed closely, as the pressure in the two cuffs was reduced, the first Korotkov sound recorded from the right arm appeared simultaneously with the first pulse wave to be recorded by the Hamilton manometer. In two records (one subject), the first sound was recorded simul-

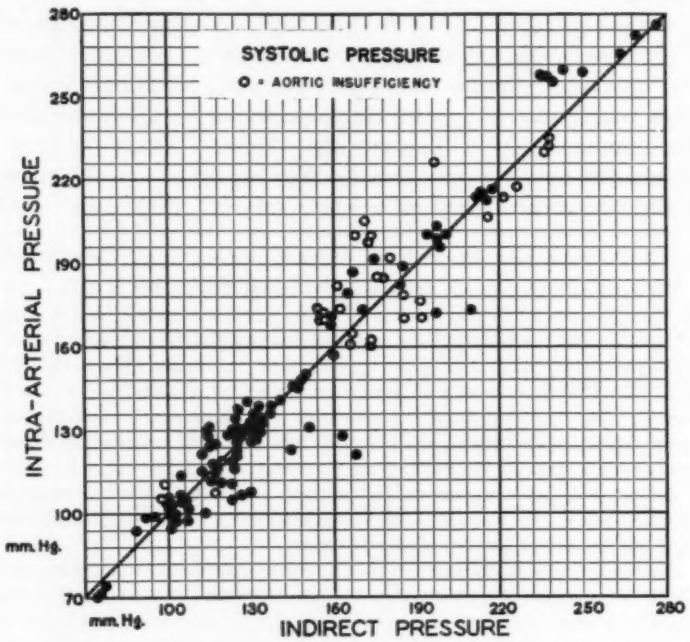

FIG. 3. CORRELATION BETWEEN AUSCULTATORY (INDIRECT) AND INTRA-ARTERIAL MEASUREMENTS OF SYSTOLIC PRESSURE

taneously with the second pulse wave which came through beneath the occluding cuff. It was concluded from these experiments that the lack of agreement between the intra-arterial and auscultatory systolic pressure readings could not be accounted for by the passage of inaudible pulse waves beneath the occluding cuff.

The *diastolic pressure* correlations are shown in Figure 8. With the

auscultatory method the pressure was measured at the first abrupt fade in the sounds (the beginning of the so-called fourth phase). Using this index, the measurements made by the auscultatory method are usually about 10 mm. Hg higher than the intra-arterial diastolic

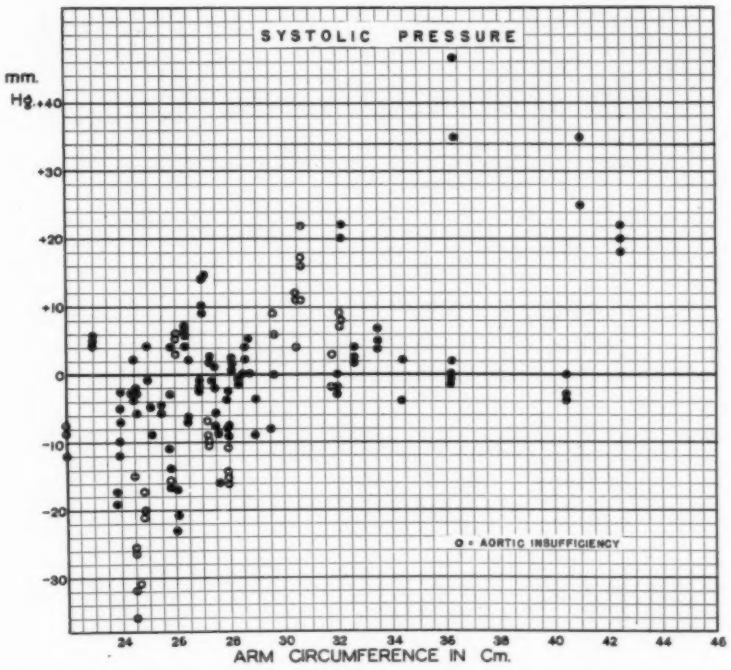

FIG. 4. DEVIATION OF AUSCULTATORY MEASUREMENTS FROM INTRA-ARTERIAL MEASUREMENTS OF SYSTOLIC PRESSURE IN RELATION TO ARM CIRCUMFERENCE

pressures. However, there is conspicuously less scattering of the figures than there was in the case of the systolic pressures.

The deviation of the auscultatory diastolic pressures from the intra-arterial diastolic pressures is plotted with respect to arm circumference in Figure 9. Excluding several cases of aortic insufficiency in which the auscultatory estimates of diastolic pressure were far too low, most

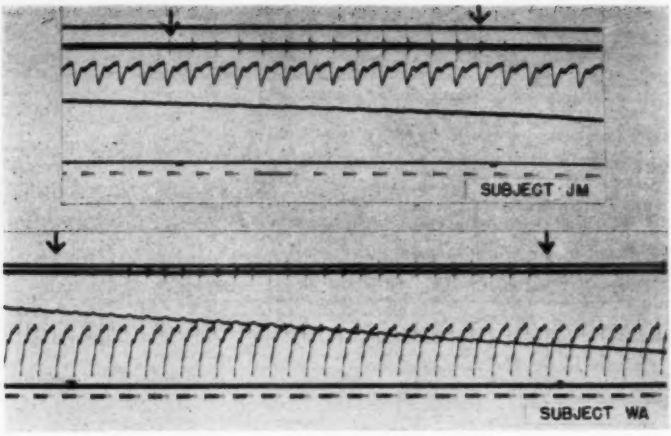

FIG. 5. PHOTOGRAPHIC RECORDS FROM TWO SUBJECTS CONTRASTING FULL PULSE WAVE (ABOVE) WITH PEAKED PULSE WAVE (BELOW)

In Subject J. M., with an arm circumference of 28.2 cm., the intra-arterial pressure determinations were 104 mm. Hg systolic, 51 mm. Hg diastolic; the graphic auscultatory determinations were 105 mm. Hg systolic, 65 mm. Hg diastolic. In Subject W. A., with an arm circumference of 24.5 cm., the intra-arterial pressure determinations were 200 mm. Hg systolic, 75 mm. Hg diastolic; the graphic auscultatory determinations were 168 mm. Hg systolic, 75 mm. Hg diastolic.

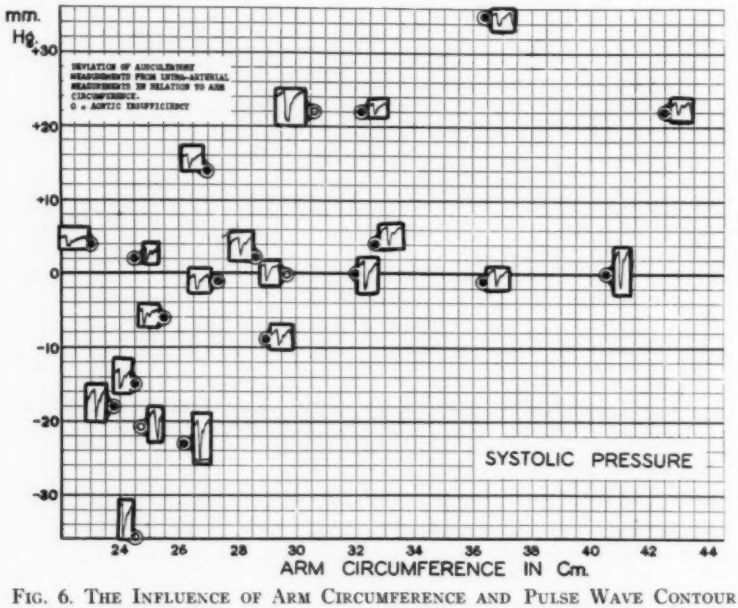

FIG. 6. THE INFLUENCE OF ARM CIRCUMFERENCE AND PULSE WAVE CONTOUR UPON THE ACCURACY OF THE AUSCULTATORY DETERMINATIONS OF SYSTOLIC ARTERIAL PRESSURE

As noted in Figure 1 the intra-arterial pulse wave tracings are inverted.

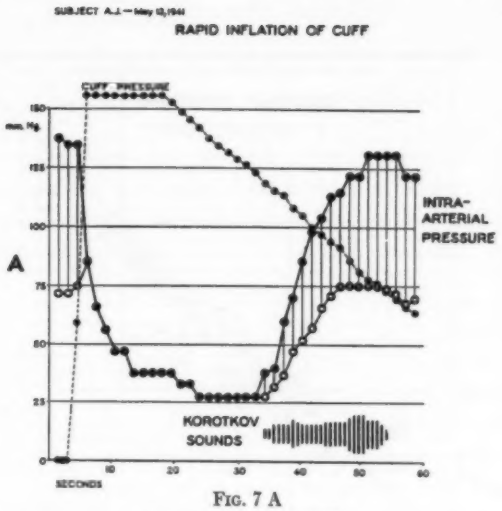

FIG. 7 A

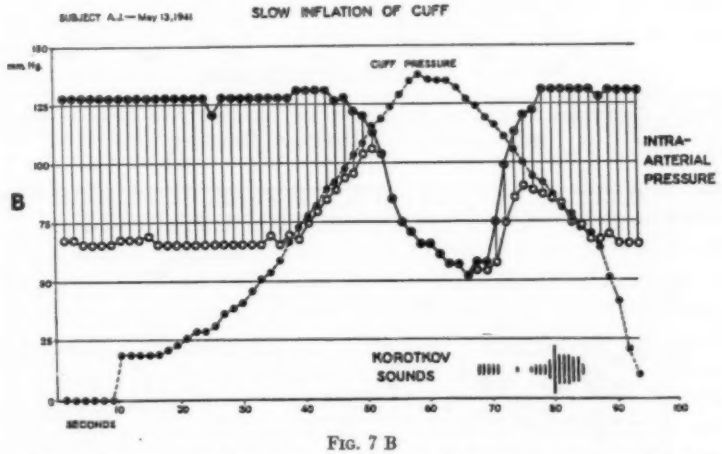

FIG. 7 B

FIG. 7. RELATION OF KOROTKOV SOUNDS TO PASSAGE OF THE PULSE WAVE BENEATH OCCLUDING CUFF

Intra-arterial pressure was measured in the left arm and the Korotkov sounds were picked up in the right arm. A standard cuff, 13 cm. in width, was placed about each arm: on the left, proximal to the needle of the manometer; on the right, proximal to the microphone. The pneumatic bags of the cuffs were connected in parallel and equal pressures entered the two cuffs. Intra-arterial systolic pressures are represented as dots, diastolic as open circles, and the pressure in the cuffs as an interrupted line. The pressures in the cuffs and in the intra-arterial tracing were measured for *every second* pulse wave. The intensity of the Korotkov sounds, as represented by the height of the deflections, is charted to scale for *every* pulse wave.

Figure 7 A is a chart of the results obtained by rapid inflation of the cuffs, and Figure 7 B the results obtained by slow inflation of the cuffs (See Addendum).

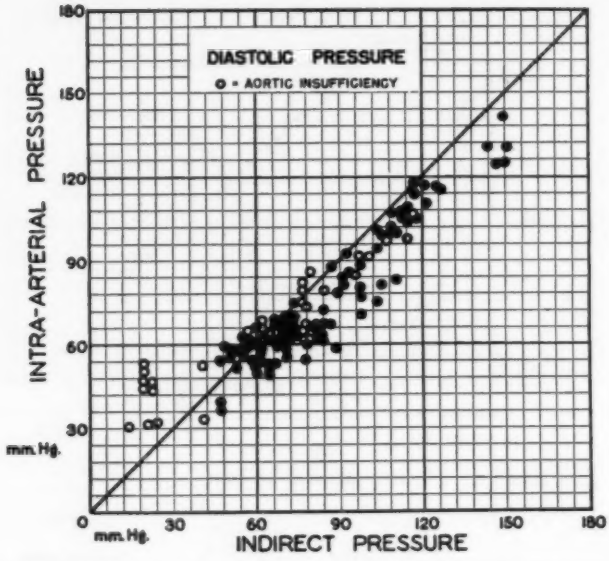

FIG. 8. CORRELATION BETWEEN AUSCULTATORY (INDIRECT) AND INTRA-ARTERIAL MEASUREMENTS OF DIASTOLIC PRESSURE

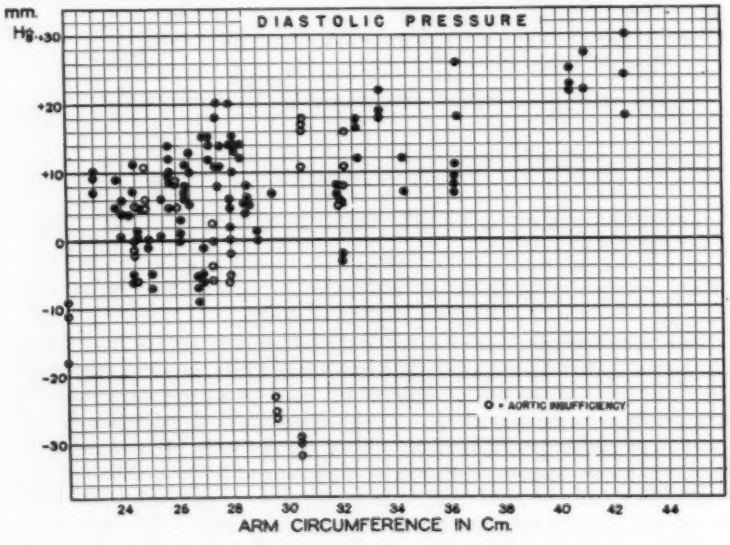

FIG. 9. DEVIATION OF AUSCULTATORY MEASUREMENTS FROM INTRA-ARTERIAL MEASUREMENTS OF DIASTOLIC PRESSURE IN RELATION TO ARM CIRCUMFERENCE

of the points fall above the line of perfect agreement. Again the points show a trend: with small arms the auscultatory readings tend to be only slightly too high (less than 10 mm. Hg) but with large arms, the positive deviation increases to between 10 and 30 mm. Hg.

DISCUSSION

Clinical measurements of arterial blood pressure should, ideally, convey a reasonably accurate estimate of the pressure, both systolic and diastolic, within the brachial artery. It would appear from the foregoing observations that in a significant number of cases this ideal is not achieved by the methods currently employed. When these experiments were undertaken it was our belief that the Korotkov criterion of systolic pressure was probably more reliable than the Korotkov criterion of diastolic pressure (beginning of fourth phase), but this has proven not to be the case.

The auscultatory estimates of diastolic pressure were, with rare exceptions, too high. The mean deviation in 101 comparisons (excluding the subjects with aortic insufficiency) was +8 mm. Hg. In view of this fact it might be supposed that the complete disappearance of the Korotkov sounds would serve as a better index of diastolic pressure than the sudden fade in the intensity of the sounds at the beginning of the fourth phase. Actually, however, this serves to diminish rather than to increase the reliability of the auscultatory estimates. The disappearance of the sounds may occur almost simultaneously with the beginning of the fourth phase, or it may be delayed until the pressure has fallen far below the intra-arterial diastolic pressure. As a result, a rather small and relatively uniform error is converted into a completely unpredictable and sometimes very large error.

It would appear from the few scattered observations on subjects with large arms (30–42.5 cm. in circumference), that the positive error of the auscultatory estimates of diastolic pressure increases approximately 3 mm. Hg for each 1 cm. increase in arm circumference. If the observed readings are corrected accordingly, the size of the error may be brought into line with the relatively uniform error encountered in subjects with arms of average adult size[5].

[5] One hundred patients were taken at random from the medical and surgical

It is a more difficult matter to apply any simple correction for the error of the auscultatory systolic pressure measurements. Here, an additional variable influences the accuracy of the results, namely, the contour of the pulse wave. At the present time, there is no simple clinical method for estimating accurately the shape of the pulse wave. In some cases (e.g., cases of aortic insufficiency) palpation of the radial pulse may be helpful, but occasionally it may be very misleading. Disregarding the contour of the pulse wave, one may offer two practical generalizations: (a) in subjects with small arms, the routine auscultatory measurements of systolic pressure are usually too low, (b) in subjects with large arms, the measurements are usually too high. Therefore, one is likely to make false diagnoses of arterial hypertension only in large or obese individuals, and false diagnoses of arterial hypotension only in small or emaciated individuals.

It may be seen in Table II that the use of the 20 cm. blood pressure cuff does not improve the accuracy of the auscultatory measurements. The readings of both systolic and diastolic pressure are frequently much too low. The wider cuff seems particularly liable to yield falsely low estimates in hypertensive patients. Experiments have not been carried out with cuffs of many different widths, but it seems likely from the observations already mentioned that the selection of a blood pressure cuff of an appropriate size for each arm is a more difficult and less satisfactory solution to the problem in adults than it was found to be in new-born infants and children (9, 7). In this connection, it is interesting to recall that the choice of a proper width cuff was found to be more difficult in older than in younger children (7); this may be attributable to the fact that the contour of the pulse wave becomes more variable as age advances from infancy to adolescence (7).

The subjects employed for the present study were for the most part relatively young adults. It is possible that in an older age group

wards of the hospital and the circumference of the right arm of each was measured at the level mentioned under *Methods*. There were 57 males and 43 females with a mean age of 42 years (16–78). The mean arm circumference of this unselected group was 27.0 cm. (16.8–42 cm.). The mean arm circumference of the 51 subjects who served for arterial pressure measurements was 27.5 cm. (22.0–42.5 cm.).

the accuracy of the auscultatory measurements would be affected by an additional factor, namely, the rigidity of the walls of the arteries.

SUMMARY

Two graphic methods were employed simultaneously to measure the arterial blood pressure in human subjects: (1) the intra-arterial method of Hamilton, and (2) an auscultatory method similar to that used in routine clinical blood pressure determinations.

Auscultatory pressure measurements were compared with intra-arterial pressure measurements 138 times in 51 adult subjects: 28 with normal or low arterial pressure, 12 with arterial hypertension, and 11 with aortic insufficiency.

The agreement between the auscultatory and intra-arterial measurements of *systolic pressure* was affected both by the size of the subject's arm and the contour of the pulse wave. In subjects with small arms, the auscultatory measurements were usually too low; in subjects with large arms, the auscultatory measurements were usually too high. In occasional subjects, the auscultatory measurements were grossly inaccurate, *e.g.*, more than 30 mm. Hg above or below the intra-arterial systolic pressure. When the subjects with aortic insufficiency and those with upper arms greater than 35 cm. or less than 24 cm. in circumference were excluded, the auscultatory systolic readings came within ± 10 mm. Hg of the intra-arterial systolic pressure in 83 per cent of the comparisons.

The auscultatory measurements of *diastolic pressure* (employing sudden fading of the Korotkov sounds as an index of diastolic pressure) were usually higher than the intra-arterial measurements. The positive deviation increased with increasing size of arm. In some, but not in all, cases of aortic insufficiency, the auscultatory measurement of diastolic pressure was much too low. Excluding the cases of aortic insufficiency, the mean deviation of the auscultatory from the intra-arterial measurements was $+8$ mm. Hg.

In some obese subjects the substitution of a wide (20 cm.) blood pressure cuff for the standard (13 cm.) cuff afforded more accurate auscultatory measurements of both systolic and diastolic pressure. In most subjects, however, the wide cuff yielded measurements which were too low.

CONCLUSIONS

The commonly employed clinical method of measuring blood pressure should not be looked upon as a truly accurate procedure. In most adult subjects it provides reasonably reliable information but in a significant number of cases the information may be quite misleading. Misinformation is particularly likely to be obtained in subjects with unusually large or unusually small arms: if the arm is small, the clinical estimate of the systolic pressure is likely to be too low, if the arm is large, the clinical estimate of both systolic and diastolic pressure is likely to be too high. The error in either direction may exceed 30 mm. Hg.

The foregoing observations must be borne in mind whenever it is necessary to come to a decision concerning the diagnostic or prognostic significance of minor depressions or elevations in the level of the blood pressure.

Statistical studies of the relation between blood pressure and body weight should take into account the influence of the circumference of the arm upon the accuracy of the blood pressure measurements.

The authors wish to express their thanks to
Miss Margot Robinson for her technical assistance.

ADDENDUM

Note on the "Auscultatory Gap"

The phenomenon known as the "auscultatory gap" which is noted at certain times and in certain patients during the measurement of arterial pressure by the usual auscultatory method has been recognized by clinicians for many years. As the pressure in the cuff is lowered, the first Korotkov sound appears and then after a variable number of audible pulse beats, the sounds fade out, to reappear again at a level above that of the diastolic pressure. In the past year, Berry (2) has reported that the occurrence of the gap is apparently related to the level of the venous pressure in the arm. He found that when the cuff was inflated with the arm in a dependent position the gap became more conspicuous; that when the cuff was inflated with the arm in an elevated position the gap could be eliminated. We have confirmed these observations in a number of our patients.

During the course of the present investigation, several records were obtained which gave graphic information concerning the occurrence of the auscultatory gap.

Charts of two such records are shown in Figure 7 of this paper. The methods employed in obtaining these records have already been described. When the cuffs encircling the two arms were inflated rapidly (Figure 7 A), so as to avoid

venous congestion distal to the cuffs, no auscultatory gap occurred as the cuffs were subsequently deflated. On the other hand, when inflation was carried out gradually (Figure 7 B), a well-marked auscultatory gap was noted during deflation. A very striking difference may be noted between the intra-arterial pressure tracings in the two records. After rapid inflation of the cuffs the intra-arterial pressure fell some 45 mm. Hg below the diastolic pressure level in the unoccluded artery; as the cuffs were deflated, the intra-arterial pressure rose steadily but the diastolic pressure below the occluding cuff never rose appreciably above the diastolic level in the unoccluded artery. After slow inflation of the cuffs the intra-arterial pressure did not fall so low, and as the cuffs were deflated the intra-arterial pressure rose rather rapidly and the diastolic pressure below the cuff reached a peak which was well above that of the diastolic pressure in the unoccluded artery. The relation between the auscultatory gap and the changes in intra-arterial pressure below the cuff may be noted in Figure 7 B.

In three of the four subjects on whom this type of experiment was carried out, an auscultatory gap was recorded after slow inflation of the cuffs. In each of these cases the curve of the intra-arterial pressure was similar to that shown in Figure 7 B. In the fourth subject, no auscultatory gap occurred. In this case, after slow inflation of the cuffs, the pressure in the occluded artery fell to a lower level than in the other cases, and the diastolic pressure during deflation showed the gradual, straight-line ascent which was observed in all four cases after rapid inflation of the cuffs.

These observations are recorded here to note the fact that prolonged partial occlusion of the veins of the arm during the inflation of a blood pressure cuff affects the arterial as well as the venous pressure distal to the cuff. The effect upon the arterial pressure may be the determining factor in the production of the auscultatory gap.

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ON THE EFFECTS OF THE INTRA-ARTERIAL INJECTION OF ACETYLCHOLINE AND PROSTIGMINE IN NORMAL MAN

A. M. HARVEY, J. L. LILIENTHAL, JR. AND S. A. TALBOT

From the Department of Medicine and the Laboratory of Physiological Optics, Wilmer Ophthalmological Institute, the Johns Hopkins University and Hospital

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The actions of the various cholinergic and anticholinesterase substances have been widely studied. Minute amounts of these compounds have an intense stimulating effect upon the cardiovascular and gastrointestinal systems, and the profound reactions which are thus produced have prevented a study of the actions of relatively high concentrations of these substances upon the peripheral neuromuscular mechanisms in man.

The use of intra-arterial injection avoids this obstacle by permitting the attainment of high concentrations of the substance in a local area without untoward systemic effects. Furthermore, the opposite uninjected extremity provides an excellent control. This method, which has proved so useful in mammalian physiology (Brown, 1937b), furnishes a means of studying the actions of substances in patients with various diseases of muscle and of the nervous system; and such studies will be reported subsequently. It is the purpose of this paper to record the effects of acetylcholine and prostigmine injected into the brachial artery of normal human subjects.

The close intra-arterial injection of minute amounts of acetylcholine (2 μg.) into mammalian skeletal muscle produces a powerful twitch equal in tension to that induced by a single maximal motor nerve volley (Brown, Dale, and Feldberg, 1936). This twitch is accompanied by oscillatory action potentials (Brown, 1937a; Brown and Harvey, 1941). In normal man, Lanari (1936) found that the injection of 40 mg. of acetylcholine into the brachial artery elicited no visible motor response. Masland and Wigton (1940) recorded the observation of a slow, irregular contraction and gross fasciculations in the

leg muscles of the cat following the injection of 0.1 mg. of acetylcholine in 1.0 cc. of distilled water into a branch of the popliteal artery. These responses were accompanied by spike potentials conducted centripetally in the *motor* nerves supplying the fasciculating muscles and recorded from the appropriate ventral roots which had been isolated centrally from the neuraxis. The fasciculations, contraction and the antidromic motor nerve potentials were all abolished by curarization.

Eserine and the related substance, prostigmine, have several characteristic actions in common upon the neuromuscular mechanism. In the eserinized muscle the tension of the twitch in response to a single maximal motor nerve stimulus is greatly enhanced. The muscle action potential under these circumstances is converted into a short asynchronous salvo indicating a repetitive response of the muscle fibers to the single stimulus. This repetitive character of the contraction process is thought to be the basis for the augmented twitch tension which is developed under the influence of eserine (Bacq and Brown, 1937; Brown, 1937a; Brown and Harvey, 1941). Eserine produces visible fasciculations in the normally innervated (Magnus, 1908) or acutely denervated skeletal muscle (Langley and Kato, 1915). These fasciculations are accompanied by spike potentials moving centripetally in the motor nerves (Masland and Wigton, 1940; Feng and Li, 1941). All eserine fasciculations and their associated motor nerve activity are abolished by curare and do not occur in a muscle whose motor nerve has been cut and allowed to degenerate (Langley and Kato, 1915). The excitation of eserinized muscle by a train of motor nerve volleys occurring at a frequency greater than six per minute results in a progressive depression of twitch tension. Stimuli applied to the motor nerve at a rate of 50 per second cause a brief contraction followed by relaxation of the muscle (Bacq and Brown, 1937; Rosenblueth, Lindsley, and Morison, 1936). That a depression of neuromuscular conduction results from the accumulation of a paralysing concentration of acetylcholine is suggested by the observation that the enhanced responses of eserinized skeletal muscle to low frequency single nerve volleys are abruptly depressed by the concurrent intra-arterial injection of a minute amount of acetylcholine (5 μg.). (Brown, Dale and Feldberg, Figure 10; 1936).

The action of prostigmine in restoring motor power to patients with myasthenia gravis is well known. In normal subjects, however, prostigmine injected intra-arterially was found to produce motor weakness. An analysis of this action, and of the effects of acetylcholine, is reported here.

METHOD

A study was made of 20 human volunteers recovering from a variety of diseases which did not involve the nervous or muscular systems. Injections were made into the brachial artery in the antecubital fossa through a cutaneous and periarterial bleb of 2 per cent procaine. After the needle had entered the lumen of the artery a proximal segment was occluded by digital compression against the humerus. After ten or more seconds of compression to allow emptying of the artery distal to the occlusion, the solution was injected rapidly within one to four seconds. At the close of the injection, the occluded artery was released to permit the reentry of blood to wash the column of injected fluid out to the periphery at a high concentration.

When acetylcholine was introduced into the artery no attempt was made to prevent its return into the general circulation because of the rapidity of its destruction in the periphery (Ellis and Weiss, 1932), and no general effects were observed. During the study of prostigmine, however, the possible cardiovascular and gastrointestinal side actions were blocked by a preceding intravenous injection of 1.0–2.0 mg. of atropine sulfate; for atropine inhibits these muscarine-like effects of prostigmine, while the nicotine-like effects of prostigmine on striated muscle are not altered by atropine. A sphygmomanometer cuff placed about the upper arm was inflated to a pressure of 30–40 mm. of mercury for one minute immediately after the injection to promote local fixation in the injected area. No unpleasant general reactions developed when these precautions were observed.

Vasomotor and sudomotor reactions and evanescent movements were observed after the injection. The subject was questioned regarding subjective sensations at the close of their development. The rapid and transient changes in motor power were estimated roughly by the strength of grip. The more prolonged changes in muscle power were measured with a recording dynamometer.

Electrical recordings of the muscle action potentials were made with two technics. Concentric needle electrodes (Adrian and Bronk, 1929) placed in the bellies of muscles of the flexor group of the forearm and of the hypothenar eminence led off the action potentials which were recorded on an ink writing Grass electroencephalographic oscillograph. The action potentials in the m. abductor digiti quinti following electric stimulation of the ulnar nerve by the method of Harvey and Masland (1941) were led to the input of a condenser coupled amplifier and recorded by means of a cathode ray oscillograph. The stimuli were square waves lasting a millisecond or more depending on the subject's threshold, and were presented singly, in pairs or in salvos by the delay circuits of Marshall and Talbot (1940). The stimulating shocks, transformer-coupled to the stimulating elec-

trodes, had slightly more amplitude than needed to elicit maximum action potentials from the muscle leads.

Preparations: Acetylcholine hydrochloride, crystalline (Merck) was freshly prepared before each injection as a two per cent solution in sterile distilled water and was injected into the brachial artery in amounts varying from 10 to 50 mg. *Prostigmin methylsulfate* (Hoffman-La Roche) was employed in a 1:2000 solution, and was injected intra-arterially in amounts varying from 0.2 to 1.5 mg.

RESULTS

Acetylcholine

Autonomic—Immediately after injection the arm below the elbow became deeply flushed, warm, and sweated profusely. These responses persisted for 10 to 15 minutes then slowly waned. These observations are in accord with those reported by Ellis and Weiss (1932) and by Lanari (1936).

Sensation—The injection was followed immediately by excruciating pain coursing down the forearm into the palm and fingers (Ellis and Weiss; Lanari). The pain attained its maximum intensity within some 5 seconds, persisted maximally for 5 seconds and then rapidly disappeared, leaving behind a sensation of warmth. The character of the pain was variously described as "burning", "tearing", or "tingling". Its quality could be reproduced best by firmly pinching the interdigital webs (Lewis, 1938).

The solution of acetylcholine, as injected, was determined with the Beckman glass electrode potentiometer to have a pH of 4.5. This concentration of hydrogen ion is said to produce pain when injected intra-arterially (Moore, Moore and Singleton, 1934). However, the hydrogen ion concentration plays no rôle in the production of pain in these observations because control studies with acetylcholine dissolved in a Na_2CO_3 buffer adjusted to pH of 6.9 produced identical reactions. Control injections of the Na_2CO_3 solution (25 mg. per l.) and of distilled water produced no effect.

Every subject stated that the pain was accompanied by a sensation of forceful flexion of the fingers, palm, and wrist described as a "drawing up". However, no movement of this sort was observed.

Motor—Simultaneously with the development of pain in the injected arm the grip power of the fingers and hand was greatly reduced so that only the most feeble and partial flexion of the fingers could be

effected voluntarily. That this transient paresis was not a voluntary reaction to the coincident pain was suggested by its persistence for 10 to 20 seconds after the pain had disappeared. There was complete recovery of normal motor power 30 to 60 seconds after injection. The rapidity of recovery prevented dynamometric recording of this effect.

We have observed no constant synchronized movements in the fingers or hand following the injection of acetylcholine. In one subject there developed a brief movement of the fingers and hand resembling the carpal spasm of mild tetany. This lasted but three to four seconds. However in four subjects there appeared in the relaxed palmar and forearm muscles brief localized twitches of insufficient tension to produce more than a slight movement of the fingers. These fasciculations appeared within the first 10 seconds after injection and lasted for 15 to 20 seconds. They occurred at a frequency of one visible fascicular twitch per one or two seconds over the entire extremity.

Prostigmine

Autonomic—Prostigmine, in the quantities injected in this study, produced a slight flush and moderate warmth of the skin. Sweating was minimal because of the prior administration of atropine.

Sensation—No subject experienced pain or the sensation of forced flexion induced by acetylcholine.

Motor—Two striking motor phenomena invariably followed the intra-arterial injection of 0.2 to 1.5 mgs. of prostigmine. Immediately after the injection, there ensued a profound weakness of all movements of the fingers, hand and wrist of the injected extremity. Maximal voluntary contraction consisted of the slightest flexion of the fingers which could be sustained only for a fraction of a second and was followed by complete involuntary relaxation of the hand. After 10 seconds rest, another such unsustained movement could be effected. In the early phase of extreme paresis, which lasted one to three minutes depending upon the size of the dose, the hand was too weak to grasp the dynamometer grip. Motor power began slowly to return after five minutes and normal power was recovered after 20 to 45 minutes (Figure 1). During the period of weakness, there was no resistance to passive movement of any of the joints; and the consistency to

palpation of the muscles of the thenar and hypothenar eminences and of the forearm was not altered. There were no sustained involuntary movements.

Within 15 seconds after the completion of the injection, the subjects described the sensation of "fluttering" movements of an involuntary nature in the muscles of the affected arm. At the same time there appeared rapid, arhythmic gross and fine fasciculations. In an area two by two cm. over the thenar eminence selected for observation,

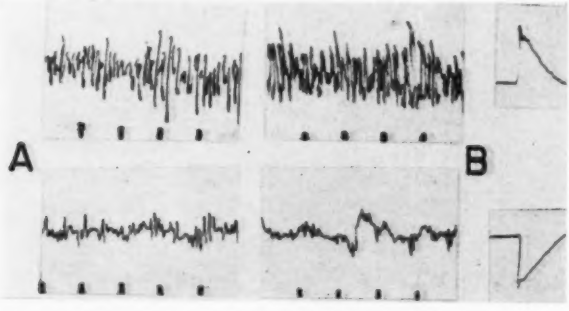

FIG. 1. Electromyogram of m. flexor pollicis brevis during maximal voluntary flexion of the thumb, recorded by a concentric needle electrode. Normal males. *A*. Upper tracing: Maximal contraction before prostigmine. Lower tracing: Maximal contraction five minutes after injection of 0.5 mg. of prostigmine into brachial artery. *B*. Upper tracing: Before prostigmine. Lower tracing: Five minutes after 1.0 mg. of prostigmine injected into brachial artery.

Time = 0.2 sec. Oscillograph calibration = 50μV.

After prostigmine the action potentials are reduced in a contracting muscle, in parallel with the weakness.

the fasciculations occurred at a rate varying from 50 to 80 per minute. The fasciculations were usually not fully developed until after the short period of maximum paresis and then persisted in slowly decreasing frequency for 10 to 30 minutes.

During the period of motor weakness following the injection of prostigmine, the muscle action potential in response to a single supramaximal motor nerve stimulus presented voltage and duration characteristics identical with those of the normal control period. However, the normal diphasic potential was converted into a repetitive response

consisting of a series of three or four spikes. The spikes were separated by approximately equal time intervals and diminished progressively

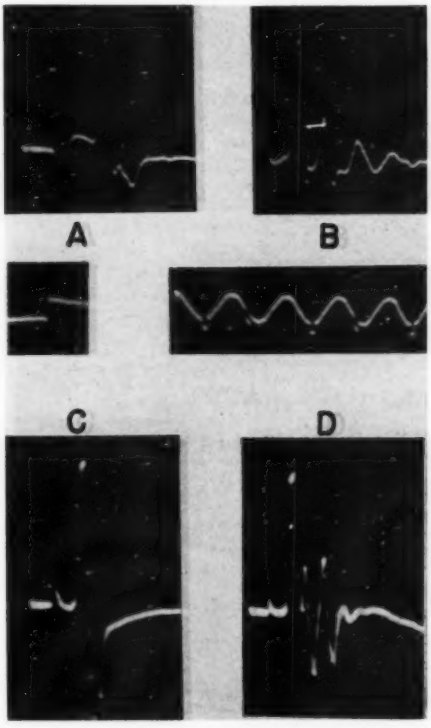

FIG. 2. Action potentials of m. abductor digiti quinti following a single supramaximal shock to ulnar nerve. *A*. Before prostigmine. *B*. Five minutes after 1.0 mg. prostigmine injected into brachial artery. *C & D*. Same procedures in another subject.

Calibration = 2 mV. Time: 1 cycle = 16.6 msec. Amplification and sweep speed are the the same in each record.

Repetitive discharge evoked by a single motor nerve volley appears after the injection of prostigmine. The voltage of the initial potentials are the same before and after prostigmine.

in voltage and duration (Figure 2). When two stimuli were given at varying intervals no repetitive response was evoked by the second

stimulus unless the interval between the stimuli exceeded 16 msec. With increasing time intervals between the stimuli, the repetitive response became more marked (Figure 3).

The most striking effect of intra-arterial prostigmine upon neuromuscular transmission was demonstrated by giving pairs of supra-

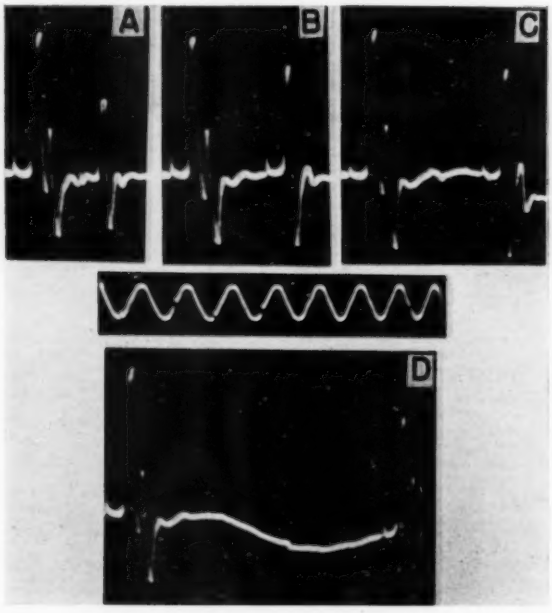

Fig. 3. Action potentials evoked by pairs of supramaximal motor nerve stimuli separated by increasing time intervals. Normal subject after intra-arterial prostigmine. Time: 1 cycle = 16.6 msec.

Repetitive discharge is fully developed in the first action potential of each pair; the repetitive discharge in the second response increases with greater separation of the paired stimuli.

maximal motor nerve stimuli separated by varying intervals of time. When the time interval between the paired stimuli was sufficiently brief, the muscle action potential evoked by the second stimulus was significantly lower in voltage and shorter in duration. At the earliest interval at which the two responses could be clearly differentiated the

depression of the second potential was greatest and with increasing intervals it rapidly became less, apparently being indirectly proportional to the time interval separating the two volleys (Figure 4). It is important to note that the second action potential has not only a lowered voltage but also a decreased duration, indicating that the fall in voltage is not the result of temporal dispersion of the fiber responses. The duration of the depression set up by a single motor

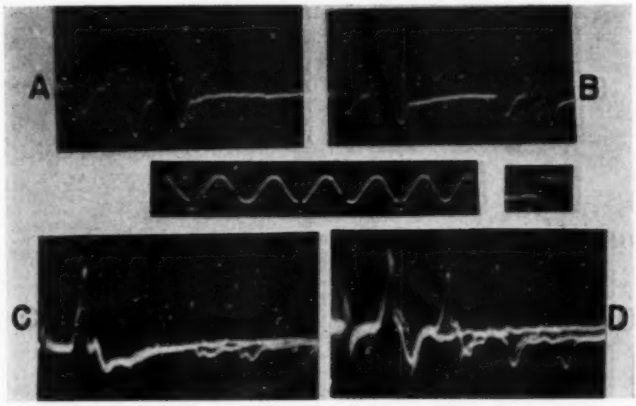

FIG. 4. Action potentials evoked by paired supramaximal motor nerve volleys. *A*. Stimuli separated by 16 msec. and *B*. by 48 msec. *C*. Same subject, five minutes after injection of 1.0 mg. prostigmine into brachial artery. Superimposed consecutive paired responses separated by 32, 48 and 64 msec. intervals, showing the progressive recovery from neuromuscular block which has almost disappeared 64 msec. after the first impulse. *D*. Same subject 20 minutes after *C*. Intervals between paired stimuli are 16, 32 and 48 msec. Neuromuscular transmission is now completely recovered 48 msec. after the first impulse. Time: 1 cycle = 16.6 msec. Calibration = 2mV.

nerve volley varied in different subjects from 80 to 600 msec. The degree of this depression of neuromuscular transmission was greatest during the first ten minutes after injection; the maximal depression of the second response approached 70 per cent. During the period when motor power was recovering, this depression was only 30 per cent (Figures 4 and 5).

One subject received 0.5 mg. prostigmine intra-arterially and

developed the usual profound local weakness and many fasciculations lasting 15 minutes. He was then given 0.4 gm. of quinine sulfate four times a day for two days and shortly after the last dose of quinine, 0.7 mg. of prostigmine was again injected into the same brachial artery. No weakness developed. There were a few scattered fasciculations in the extremity in contrast to the extensive fasciculations which had occurred before quinine.

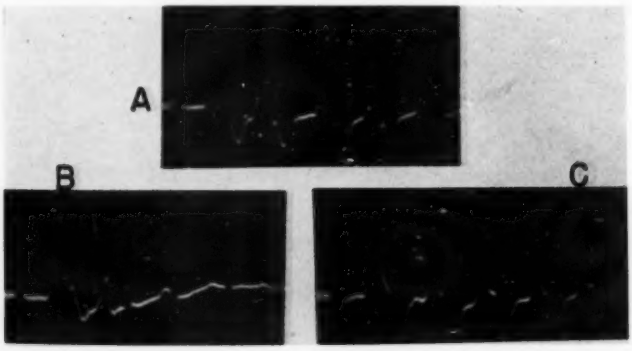

FIG. 5. Same experiment as Figure 4 but the muscle has been stimulated with a series of five supramaximal motor nerve volleys at 16 msec. intervals. *A*. Equal potentials before prostigmine. *B*. Deep and increasing neuromuscular block five minutes after prostigmine. *C*. Almost complete recovery 25 minutes after prostigmine.

Prostigmine and Acetylcholine

In three subjects intra-arterial injection of 0.3 to 0.5 mg. prostigmine was performed; and after 10 to 15 minutes when the fasciculations had disappeared and recovery of motor power was almost complete, acetylcholine in amounts varying from 5 to 40 mg. was injected into the same artery. The usual vasodilation and pain resulted, but owing to the prior administration of atropine, sweating was minimal. Immediately after the injection of acetylcholine, there was a return of profound weakness and many fasciculations, both of which lasted for one to two minutes and then rapidly disappeared during the next three to five minutes. As with acetylcholine alone there was an accompanying sensation of forceful flexion of the fingers, hand and

wrist without any actual motion observed. This sensation lasted for 15 to 30 seconds. The preceding injection of prostigmine apparently did not prolong the sensory manifestations of acetylcholine, but the decrease in voluntary motor power was greater and of longer duration.

DISCUSSION

The observed effects of intra-arterially injected acetylcholine in man upon the sweat glands and the peripheral vascular bed agree with the present concepts of the functions of the cholinergic nerves.

The subjective sensory patterns elicited by relatively high concentrations of acetylcholine attained at the periphery were not anticipated from any consideration of its known actions. The diffuse and intense pain must result from generalized stimulation of nerve endings subserving pain. The brief duration of the sensation suggests that a high concentration of acetylcholine is necessary to stimulate these nerve endings and this concentration may well be greater than any occurring under physiological conditions. The constantly occurring subjective sensation of forced flexion of the extremity without actual movement suggests that even the more complicated intramuscular spindles subserving proprioception are susceptible of stimulation by relatively great concentrations of acetylcholine. The possibility exists that the impulses moving centripetally in the motor nerves may evoke activity of the adjacent sensory neurones either at the periphery or within the spinal cord. We have no evidence to indicate that sensory nerve endings are stimulated by acetylcholine under normal conditions; but it is apparent that certain nerve endings or fibers do respond to the high concentrations of acetylcholine which have been observed in this particular investigation. Further analysis of the possible chemical mediation of sensory impulses must begin with a study of dorsal root electrical activity during peripheral injection of acetylcholine into an area deprived chronically of its motor innervation.

The motor phenomena of paresis and fasciculations occurred only transiently and feebly with the doses of acetylcholine which were employed. With prostigmine, however, these effects were much more prolonged and profound and have lent themselves, therefore, to more

detailed analysis. It is believed that the prostigmine paresis results from the inhibition of cholinesterase which permits the concentration of acetylcholine to rise to a paralysing level. The observations upon the injection of acetylcholine during that period when the extremity was recovering from the prostigmine effect support this view. The acetylcholine reaching the periphery, where some residual prostigmine effect remained, produced an immediate recurrence of the profound paresis and more frequent and extensive fasciculations than had been obtained during the height of the prostigmine effect. And further, the degree of the weakness and the rapidity and extent of the fasciculations were much greater than those produced by an equal amount of acetylcholine injected alone.

Eserine, apart from its effect on neuromuscular transmission, increases the response of directly stimulated skeletal muscle (Brown and Harvey, 1941). And, if the assumption of parallel actions of eserine and prostigmine be valid, there is no reason to suppose that prostigmine has any direct depressant action on muscle fiber contraction. We have presented evidence that a depression of neuromuscular transmission follows the passage of a single volley to the prostigminized effector. The depression of neuromuscular conduction is not a steady state for a single volley evokes a muscle action potential, equal in magnitude to the normal control; but there follows a brief period of depression of neuromuscular transmission which is proportional in depth to the degree of the prostigmine effect then existing. This transient depression is demonstrated by the reduction in the magnitude of the muscle action potential resulting from the second of a pair of supramaximal nerve stimuli given at close intervals. (Figures 3, 4 and 5). By plotting the relation of the action potential to the time interval separating the paired stimuli, the course of the subsidence of the neuromuscular depression may be determined (Figure 6). This depression extends beyond the normal relative refractory period of the muscle fibers which is certainly less than 16 msec. Despite certain objections (Eccles, 1936) there is much evidence to support the belief that the events occurring at the neuromuscular junction with the passage of a motor nerve impulse may be related to the liberation of acetylcholine and its rapid hydrolysis by a cholinesterase (Brown, 1937b; Nachmansohn 1940). If the liberated acetyl-

choline is protected from hydrolysis by prostigmine, it may persist in depressing concentrations at the neuromuscular junction; and recovery of transmission across the junction must then depend largely upon diffusion of acetylcholine from the region of the motor end plate. The velocity of recovery from the prostigmine neuromuscular depression is compatible with such a process. Eccles, Katz and Kuffler (1941) have shown that in the cat's soleus muscle eserine prolongs the end-plate zone refractory period from the normal of 2.0 msec. to

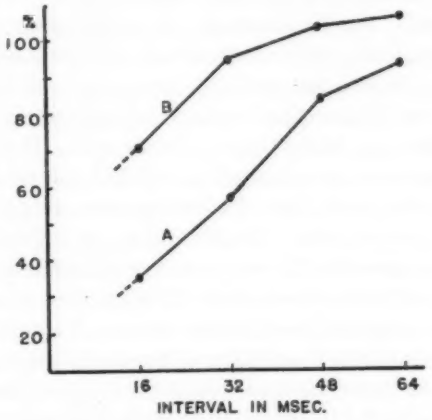

FIG. 6. Recovery curve of the second response of a pair. The voltage of the second response of a pair, expressed as percentage of the first, is plotted against the interval between the two stimuli.

Curve A: during profound paresis five minutes after the injection of 1.0 mg. of prostigmine.

Curve B: twenty minutes later when recovery of motor power is almost complete.

5.0 msec.; this is consonant with a prolongation of the entire recovery process such as that described in these experiments.

The transient neuromuscular block in a prostigminized preparation set up by a single nerve volley and the increasing block produced by a train of stimuli resemble in many respects the effects of partial curarization. Partial curarization, however, reduces the amplitude of the muscle action potential evoked by the first maximal motor nerve volley while prostigmine has no effect upon it. The recovery

from the increase in the neuromuscular depression which follows the passage of a single nerve volley across the neuromuscular junction under the influence of curare requires from one to two seconds (Brown, 1938; Harvey and Masland, 1941b); recovery from prostigmine depression occurs much more rapidly, and in most instances is complete within 100 msec.

It seems probable that prostigmine produces weakness by protecting acetylcholine from hydrolysis until a paralysing concentration is attained. This explanation gains support from the finding that quinine prevented the development of prostigmine paresis. For quinine has been shown to block not only the *excitation* of skeletal muscle by acetylcholine but also the *depression* of muscle response usually induced by acetylcholine injected into the artery of an eserinized muscle (Harvey, 1939; Oester and Maaske, 1939). This depression of response in an eserinized muscle induced by acetylcholine has been shown to result from the development of paralysing concentrations of acetylcholine (Brown, Dale, and Feldberg, 1936). And since quinine prevents the depression by prostigmine, it furnishes indirect evidence that the prostigmine effect results from an abnormal accumulation of acetylcholine at the neuromuscular junctions. Thus one certain factor in the production of paresis by prostigmine is its depression of neuromuscular transmission; and the evidence suggests that this follows the development of paralysing concentrations of acetylcholine released at the neuromuscular junction during either voluntary contraction or activity produced by electrical stimulation of the motor nerve.

There may be other mechanisms contributing to the weakness. One theoretical possibility, for which we have no relevant data, is that the antidromic impulses travelling centripetally in the motor nerves and the activity of the sensory nerves during the fasciculations summate to set up both a transient refractoriness and also a more prolonged "central inhibitory state" of the motoneurones in the ventral horns of the spinal cord (Creed *et al.*, 1932; Eccles, 1936). The observed fact that a single supramaximal stimulus to the motor nerve evokes a muscle action potential of normal amplitude excludes the possibility that the motor nerve itself is in a persistent refractory state.

The repetitive muscle action potentials in response to single nerve

volleys in eserinized muscle have been shown to occur in the prostigminized muscle of man. The decreasing voltage of the regularly occurring spikes initiated by a single volley is of the same order as that described in the eserinized inferior oblique muscle of the cat; and the absence of a repetitive response to the second of a pair of stimuli separated by a brief time interval corresponds to the responses found in the tibialis anterior of the cat (Brown, 1937a; Brown and Harvey, 1941; Feng and Li, 1941). Brown (1937b) has presented evidence which suggests strongly that the repetitive eserine response is the result of the persistence of the transmitting agent at the neuromuscular junction. Recently Eccles, Katz and Kuffler (1941) have demonstrated that the depolarization of the end-plate-muscle system produced by a single motor nerve volley is prolonged by eserine. "Persistence of the transmitter" and "prolongation of the end plate potential" may be simply a unitary process described in different terms; and both are compatible with repetitive activity of the neuromuscular mechanism.

Denny-Brown and Pennypacker (1938) have presented the evidence which makes it seem likely that fasciculation is the response to stimulation of an entire motor unit with the synchronous contraction of its related muscle fibers producing the visible brief movement. The probable locus of the stimulatory action of eserine and prostigmine in the production of fasciculations is indicated by several data. Acute section of the motor nerve has no effect on eserine fasciculations so that the origin of the impulse must lie distal to the ventral horn cells; eserine will not produce fasciculations in a muscle whose motor nerve has degenerated, so that the muscle fiber alone is not sufficient for the development of eserine fasciculations (Langley and Kato, 1915). The synchronous firing of the whole motor nerve unit makes it unlikely that the impulse originates in a single nerve ending and is then transmitted to the other fibers in the unit by means of an axon reflex, although there are no data bearing upon this possibility. By exclusion, then, the site of stimulation of the motor unit by eserine might lie distally in the nerve fiber, perhaps at or adjacent to the point of division of the motor axon into its terminal branches. This suggestion is implicit in the discussion of Masland and Wigton (1940). There is, however, a discordant fact which at first would appear to render this

concept untenable in the light of present knowledge. And that is the abolition by curare not only of fasciculations but also of the accompanying antidromic motor nerve potentials, in doses too weak to block neuromuscular transmission (Langley and Kato, 1915). However, the action of curare at the neuromuscular junction is to raise the threshold to stimulation by acetylcholine (Brown, Dale and Feldberg, 1936). This might well be its action upon motor nerve which appears to respond under normal conditions to an adequate concentration of acetylcholine (Masland and Wigton, 1940). Thus curare may block the stimulating action of acetylcholine and not affect the conduction and electrical threshold of the axon (Fromherz, 1933). The role played by acetylcholine in the conduction of the nervous impulse has been reconsidered by Nachmansohn and Meyerhof (1941) who demonstrated the localization of significant concentrations of cholinesterase in the sheath of the squid giant axon. If the metabolism of acetylcholine is related to axonal potential changes then the prostigmine fasciculations might result from inhibition of cholinesterase activity in the axon sheath. The assumption that the origin of the antidromic impulses accompanying fasciculations lies distally in the nerve fiber requires that this region be particularly susceptible to stimulation by acetylcholine. And this may well be the case, for at the point where the axon divides into its terminal branches, the ratio of axon surface to axon volume is greatest and the surface area is apparently most concerned in the acetylcholine mechanism. The effect of quinine in depressing prostigmine fasciculations may be similar to the curare effect; but in addition to its curariform inhibition of neuromuscular transmission it has also a depressant action on the electrical excitability of peripheral nerve (Graham, 1935).

Lloyd (1941) has recently shown that following the stimulation of a ventral root there appear in it centripetally moving spike potentials which, from their time relations, might well result from the stimulation of the motor nerve endings by the contraction of the muscle fibers in which they terminate. These antidromic motor nerve potentials are depressed by curare *pari passu* with the depression of neuromuscular transmission. This represents the first indication that, retrograde conduction across a neuromuscular junction may occur and introduces the possibility that the prostigmine fasciculations and

their associated centripetally moving impulses in the motor nerves result from primary excitation of muscle fibers. However, this seems unlikely because eserine fasciculations are abolished with doses of curare too small to block antegrade neuromuscular transmission. (Langley and Kato, 1915).

We are greatly indebted to Dr. Wilhelm C. Hoffman who recorded the action potentials in Figure 1.

SUMMARY

1. The effects of acetylcholine and prostigmine upon motor power and neuromuscular transmission in the hand of normal man have been studied by injection of these drugs into the brachial artery.

2. Acetylcholine, in amounts varying from 10 to 50 mg., produces a) profound stimulation of the cholinergic nerves, b) severe pain and a sensation of forceful flexion in the motionless extremity and c) transient paresis of motor power.

3. Prostigmine, in amounts varying from 0.2 to 1.5 mg. produces a more prolonged paresis of the injected extremity during which period there are innumerable visible fasciculations in the muscles of the injected arm.

4. The neuromuscular block produced by prostigmine has been analysed by means of electromyographic studies of the muscle action potentials evoked by supramaximal stimulation of the ulnar nerve. This block, which appears only after activity of the neuromuscular junction, is dissipated spontaneously and rapidly in most individuals within 100 msec. The neuromuscular block created by prostigmine has been contrasted with that following partial curarization.

5. These phenomena, interpreted in terms of current physiological concepts, result from a distortion of normal neuromuscular transmission.

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OBSERVATIONS ON THE NATURE OF MYASTHENIA GRAVIS

The Phenomena of Facilitation and Depression of Neuromuscular Transmission

A. M. HARVEY, J. L. LILIENTHAL, JR. and S. A. TALBOT

From the Department of Medicine and the Laboratory of Physiological Optics, Wilmer Ophthalmological Institute, the Johns Hopkins University and Hospital

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In a recent communication, Harvey and Masland (1941 b) described a depression of neuromuscular transmission after activity of the junction in patients with myasthenia gravis, which was similar to that recorded after the partial block in neuromuscular conduction produced by curarizing agents such as quinine methochloride, erythroidine, and crude curare extract. In these patients, however, there was no demonstrable block at the neuromuscular junction to the passage of a single nerve volley. Using this same method of study, we have extended these observations in five more patients suffering from myasthenia and several new facts have been recorded. In three of the patients a single maximal nerve volley was able to excite only a portion of the total number of muscle fibers innervated. In one of these, a single response was followed by transient facilitation or recruitment of neuromuscular transmission, and in the others by a profound degree of depression. It is the purpose of this paper to point out the occurrence of this process of facilitation, to compare this phenomenon with the depression described, and to show how these abnormal physiological characteristics appear in patients with myasthenia gravis of various grades of severity.

Facilitation and depression at the neuromuscular junction have been described in animal experiments during partial block induced by small doses of curare. Bremer and Homès (1932), working with partially curarized frogs, gave a detailed description of what was called *addition latente*. Every nerve impulse arriving at the neuromuscular junction

leaves behind it a process susceptible of summation, so that with repeated impulses a certain liminal value is attained which excites the contraction of more muscle fibers than are excited by a single maximal nerve volley. Brown (1938) has extended these observations and has shown that this period of facilitation of neuromuscular conduction, resulting from the passage of a single nerve volley, lasts for 50 to 60 msec. Then there follows a period of depression of neuromuscular conduction which lasts for more than one second. Thus, there are two antagonistic processes set up by activity at the neuromuscular junction, the one tending to facilitate the passage of subsequent impulses and the other of longer duration having the opposite effect. Both of these phenomena can be demonstrated in the myasthenic patient.

In the fowl (Brown and Harvey, 1938) a single maximal motor nerve volley can excite only 75 to 80 per cent of the muscle fibers. A second stimulus given within a short period of time causes a larger portion of the muscle to contract. This naturally occurring partial neuromuscular block is accentuated by feeding chicks on a diet low in calcium. In growing goats a similar neuromuscular block is produced by a diet low in calcium (Brown and Harvey, 1940). In contrast to the block of partial curarization, depression is evident regardless of the interval between nerve stimuli.

The phenomena of facilitation and depression seen in the myasthenic patient have been analysed and will be compared in detail with similar phenomena seen in animal experiments, in an effort to throw more light on the nature of myasthenia gravis.

METHODS

In these experiments the muscle action potentials of the abductor digiti quinti in response to supramaximal stimulation of the ulnar nerve have been studied by the method described by Harvey and Masland (1941 a). The methods of injection and recording have been described (Harvey, Lilienthal, and Talbot, 1941).

MATERIAL

Patient B. W. (H.L.H. unit #55551)—a fourteen-year-old colored girl who had mediastinal tuberculosis at four and pleurisy with effusion at five but subsequently healed her tuberculous lesions and developed normally. In July, 1939, she noted ready fatiguability and, particularly, weakness of her legs. Increasing ptosis,

difficulty in chewing and swallowing, and further loss of power in her extremities developed in the autumn of 1939. Her weakness was found to disappear with adequate doses of prostigmine. She underwent a complete spontaneous remission for one month in January, 1940, but when the symptoms reappeared, she required 1.25 gm. of guanidine hydrochloride a day. After a course of guanidine therapy, her regime was changed to prostigmine, 45 mg. a day. During May, 1941, she again underwent a spontaneous remission and for two months required no medication. The electrical studies were undertaken at this time.

Patient P. C. (Unit #225775)—a thirty-three-year-old colored farmer who, in July, 1940, first noticed rather sudden onset of diplopia and weakness of his legs. A month later, following an upper respiratory tract infection, the weakness became generalised and progressed so rapidly that by February, 1941, he was unable to raise his head, bring his hands to his face, or even approximate the first and second fingers. Transient diplopia was the only demonstrable weakness of the muscles innervated by the bulbar cranial nerves. Prostigmine caused a dramatic return of power but he required at least 240 mg. a day to permit him to get out of bed and feed himself.

Patient J. S. (Unit #221400)—a fifteen-year-old white schoolboy who had been quite healthy until August, 1940, when he first noted difficulty in whistling and a little later experienced increasing difficulty in phonation. His voice tired readily with continued talking. There was no weakness elsewhere. When studied in February, 1941, he was found to have smoothing and weakness of the facial musculature, a nasal voice, weakness and ready fatigue of the soft palate. There were no other neurological abnormalities. His speech difficulty disappeared ten minutes after the subcutaneous injection of prostigmine and he was normal in all respects when receiving 15 mg. of prostigmine six times a day or 1.75 gm. of guanidine hydrochloride combined with ephedrine.

Patient R. C. (Unit #212927)—a twenty-six-year-old white housewife who, in May, 1940, during the last week of her sixth pregnancy, noted the sudden onset of thickness of speech and difficulty in swallowing. This was followed by transient ptosis and diplopia. She has never had any weakness of her extremities or trunk. Subcutaneous injection of prostigmine gave immediate relief from her myasthenic symptoms and she has had fluctuations in her prostigmine requirement but usually requires 15 mg. six to seven times a day in combination with ephedrine.

Patient R. L. (Unit #255345)—a twenty-eight-year-old white graduate student experienced the sudden onset of diplopia, ptosis and strabismus in August, 1940. Two months later she developed progressive weakness of her arms and legs which was followed shortly by nasal speech and difficulty in swallowing. She first received prostigmine in January, 1941, with profound but transient improvement in

strength. During the spring and summer of 1941, her myasthenia progressed steadily and at the time of examination 240 to 300 mg. of prostigmine a day orally had proven insufficient and she was then receiving 1.5 mg. of prostigmine subcutaneously every two to three hours. Even this dosage did not improve her strabismus and weakness of the extraocular muscles.

RESULTS

Facilitation at the neuromuscular junction: Patient B. W. has shown in each experiment a process of facilitation which varied little from day to day. When prostigmine was omitted there was always a demonstrable degree of neuromuscular block present as evidenced by by the low amplitude of the muscle action potential in response to a single supramaximal motor nerve stimulus. This potential ranged from 4.7 to 5.9 mV. The values in normal individuals vary from 6 to 9.9 mV. When a second supramaximal nerve stimulus was given within less than 60 to 70 msec. after the first, the size of the muscle action potential evoked was always greater than that in response to the first nerve impulse (fig. 1). The sooner the second volley followed the first, the greater was the amplitude of the resulting muscle action potential which in one experiment was 22 per cent greater than the first when the interval between the two was 16 msec. As the two stimuli were separated further, the relative increase in the potential of the second response became smaller and at 70 msec. the depression of the second response, which has previously been described by Harvey and Masland (1941 b), became evident. Figure 6 shows the time course of this process of facilitation. Coincident with the increase in amplitude of the second muscle action potential, there was a corresponding increase in its duration, indicating that more muscle fibers responded to the second nerve volley.

The facilitation and depression of responses to paired stimuli observed in the myasthenic patient B. W. resembled very closely the similar phenomena described by Brown (1938) in the muscle of the cat under the influence of a small dose of curarine. The similarity vanished, however, when the responses to a rapid train of stimuli were examined. In the curarized cat muscle a rapid train of stimuli at a frequency of 50 per second evoked an enhanced response to the second stimulus, but subsequent stimuli in the train evoked responses which decreased steadily in size (Brown, 1938). In the patient B. W. a

rapid train of stimuli at a frequency of 30 or 60 per second (16 and 32 msec. intervals) evoked responses which increased in amplitude until a maximum was reached. In one experiment there was a progressive increase from 5.6 to 7.6 mV. in the responses to four nerve stimuli 16 msec. apart. The fifth response showed no further rise in voltage. This represented a facilitation of 32 per cent and demonstrated that initially a single supramaximal motor nerve stimulus was

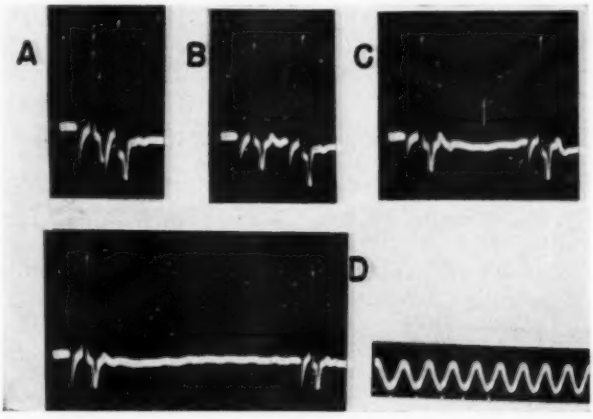


FIG. 1. Patient B. W. Action potentials of the m. abductor digiti quinti evoked by supramaximal paired stimuli to the ulnar nerve. No prostigmine for 52 hours. A. Interval = 16 msec. Second response is 119 per cent of the first. B. Interval = 32 msec. Second response is 115 per cent of the first. C. Interval = 70 msec. Second response is 99 per cent of the first. D. Interval = 160 msec. Second response is 87 per cent of the first. Time: 1 cycle = 16.6 msec.

The second of a pair of maximal stimuli evokes a greater response when it follows the first in less than 70 msec. At greater intervals a depression of the second response appears.

able to excite a response in no more than 68 per cent of the muscle fibers innervated. The same process was apparent when the stimuli were delivered 32 msec. apart. Figure 2 illustrates the character of the facilitation.

The initial facilitation without subsequent depression of responses to a rapid train of stimuli seen in the patient B. W. is similar to the facilitation of neuromuscular conduction which Brown and Harvey

(1940) found in a kid and in chicks fed a diet deficient in calcium. In these animals there was progressive enhancement of the first five or six responses to a train of stimuli until a relatively normal voltage was reached; no subsequent depression of following responses in the train developed. Thus neuromuscular transmission in the patient B. W. had characteristics in common with those produced in animals both by curare and by low calcium diets.

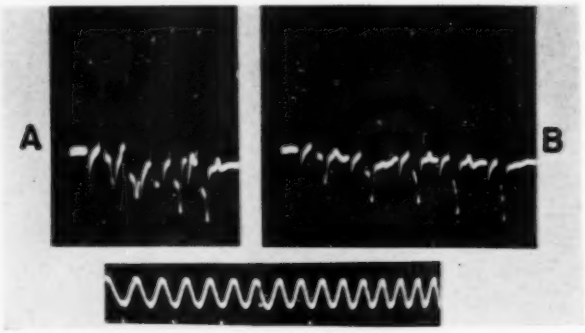


FIG. 2. Patient B. W. during the same period as Fig. 1. A. Action potentials evoked by a train of stimuli separated by 16 msec. intervals. Assigning the value of 100 per cent to the first response, the subsequent responses gain in voltage 116 per cent, 130 per cent, 137 per cent and 132 per cent consecutively. B. Same as A but at 32 msec. intervals. Gain in voltage is 120 per cent, 121 per cent, 127 per cent and 127 per cent. Time: 1 cycle = 16.6 msec.

Facilitation of consecutive responses to a train of maximal stimuli.

This patient, one of a series with myasthenia gravis, was the first in whom the muscle action potential fell well below the normal range, and in whom an improvement in the response of the muscle was brought about by repetitive stimulation. It was, therefore, of considerable importance to compare the degree of this improvement with that resulting from the administration of prostigmine. Following the administration of one mg. of this drug intramuscularly, there was a striking increase in the voltage of the response to the initial nerve volley resulting in almost complete abolition of the facilitation just described (fig. 3). In one experiment the voltage of a single response increased from 5.9 mV. to 7.5 mV. after the injection of prostigmine.

In the same experiment before the drug was given the amplitude of the potential could be increased from 5.9 mV. to 7.6 mV. by four nerve stimuli each separated by an interval of 16 msec. From this one may infer that there existed initially a degree of neuromuscular block sufficient to prevent the response of about 30 per cent of the muscle

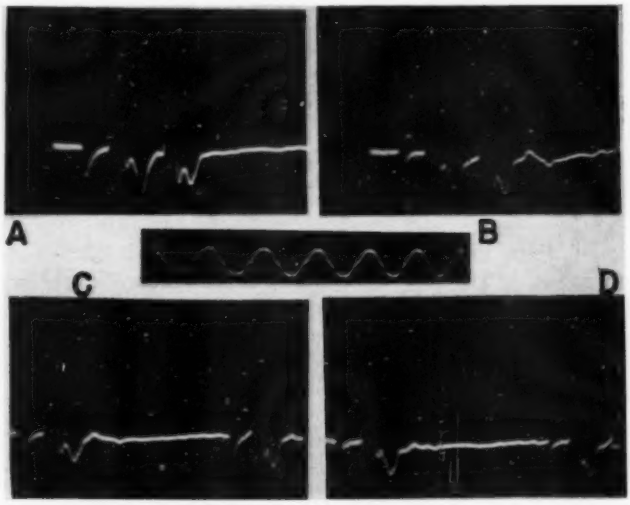


FIG. 3. Patient B. W. Ten hours after prostigmine. A. The facilitation of the second of a pair of responses to supramaximal stimuli 16 msec. apart is 20 per cent. The potential of the first response is 6.0 mV. C. Stimuli are 64 msec. apart. The potentials are both 5.9 mV. B. Twenty minutes after 0.75 mg. prostigmine subcutaneously. The potential of the first response has risen to 7.5 mV. and the second response is 103 per cent of the first, a normal relationship. D. Twenty minutes after prostigmine the pontentials have risen equally to 7.3 mV.

Prostigmine by repairing the defect in neuromuscular conduction increases the initial action potential and facilitation disappears.

fibers to a maximal motor nerve volley. This block could be abolished completely either by the passage of four volleys across the junction or by the administration of prostigmine.

In this patient, as in those described by Harvey and Masland (1941 b), when the two stimuli were separated by an interval of more than 70 msec. the potential in response to the second was smaller than

the first. (Figs. 1 and 6) This depression of the second response was also abolished by the action of prostigmine. Thus, when the effects of this drug were evidenced by improvement in the strength of the patient, the responses to two nerve volleys given at any interval greater than 16 msec. as well as the responses to trains of stimuli at frequencies near 60 per sec. were always approximately equal in size.

The muscle potentials were recorded also with greatly increased amplification in an effort to demonstrate the repetitive discharge to a single nerve volley which occurs in the normal human muscle after treatment with prostigmine (Harvey, Lilienthal, and Talbot, 1941). But repetitive response did not occur in the myasthenic muscle under the influence of prostigmine.

The Degree of Depression in Severe Cases: Patient P. C. of this series was suffering from extremely marked weakness of his extremities. It was, therefore, of great interest to study in detail his action potentials as contrasted with those of the patient B. W. just described.

The voltage of the muscle action potential in response to a single maximal motor nerve stimulus was 6.3 mV., a value within the limits recorded in a series of normal individuals. Twenty minutes following the injection of two mg. of prostigmine into the brachial artery, the potential increased to 7.5 mV. and there was a considerable increase in motor power of the injected hand. No repetitive discharge to a single stimulus could be recorded even with a high degree of amplification.

When two nerve volleys were given at varying intervals apart, the potential in response to the second was always smaller. This depression (fig. 7) increased rapidly as the interval was lengthened until the second potential was only 27 per cent of the first when the two were 350 msec. apart. Following this, the depression remained essentially the same over a long period and at 1.975 sec. the second response was still only 44 per cent of the first. This transmission curve is rather similar to that recorded in patient B. W. (fig. 6).

Prostigmine (two mg. in the brachial artery) caused some diminution in the depression, but the potentials never attained normal values as they had in the other patients studied (fig. 4G). The transmission curves indicate that prostigmine improved neuromuscular conduction.

When a short train of volleys was given, there was a very rapid

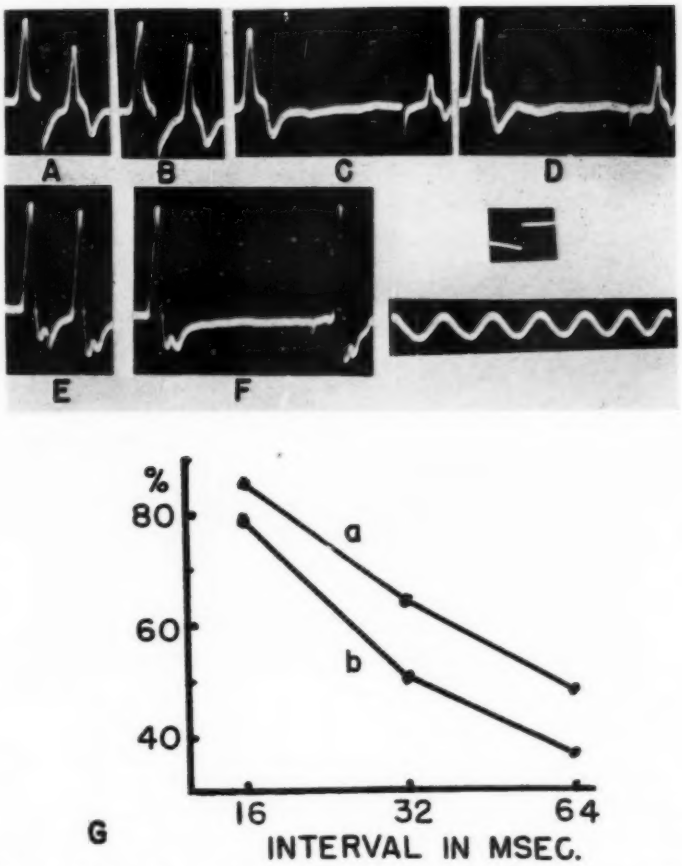


FIG. 4. Patient P. C. Prostigmine had been withheld for 72 hours. A. Paired stimuli 16 msec. apart. B. Same as A 10 minutes after the injection of 2.0 mg. of prostigmine into the brachial artery. C. Paired stimuli 64 msec. apart; before prostigmine. D. Same as C 10 minutes after prostigmine. E. and F. Normal subject showing equal responses to paired stimuli at 16 and 64 msec. intervals. Calibration = 2.0 mV. Time: 1 cycle = 16.6 msec. G. Transmission curves of P.C. a) after prostigmine; b) before prostigmine.

Prostigmine increases the response to a maximal stimulus and decreases the depression of the second response to a pair of stimuli.

decline in the successive muscle action potentials which resulted (fig. 5A). Thus the fourth potential was only 14.5 per cent of the first. There was a very pronounced improvement after the administration of prostigmine (fig. 5B), but the amplitudes of the potentials were still far below normal. Twenty minutes after the injection of prostigmine into the brachial artery, the amplitude of the fourth potential was only 41.2 per cent of that of the first.

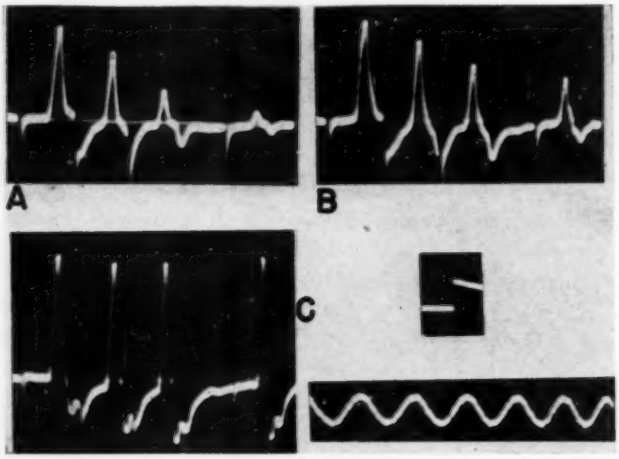


FIG. 5. Patient P. C. A. Train of four stimuli at 16 msec. intervals before prostigmine. B. Same stimuli 10 minutes after injection of 2.0 mg. prostigmine into brachial artery. C. Same train of stimuli in normal subject. Calibration = 2.0 mV. Time: 1 cycle = 16.6 msec.

Prostigmine improves neuromuscular conduction so that the progressive depression of responses to a train of stimuli is lessened.

The muscle action potentials in three other patients with myasthenia gravis have been recorded. In two of these the weakness involved only muscles innervated by cranial nerves, and there was no weakness of the extremities.

In patient J. S. the voltage of a single maximal response was 9.5 mV. and in patient R. C., 7.2 mV. Both of these values are well within the limits of normal. Two-volley transmission curves, plotted for each of these cases, in no way differed from the normal. However,

in both instances the potentials in response to a *train* of maximal nerve volleys showed the characteristic decline in the voltage of the successive responses. A train of stimuli given at 16 msec. intervals resulted in the following responses (in mV.): patient J. S.—9.1, 8.8, 7.9, and 7.4; and in patient R. C.—7.0, 7.0, 6.8, 6.5, and 6.0.

In the fifth patient, R. L., the potential of a single maximal response, while prostigmine therapy was withheld, was 3.5 mV. A two-volley transmission curve showed a progressive fall in the potential of the second response until at 216 msec. the second response was but 69 per cent of the first. After the subcutaneous administration of 2.5 mg. of prostigmine, the percentage depression of the second response was unaltered but the voltage of the response to the initial stimulus had risen to 4.7 mV. Prostigmine did, however, abolish the depression in a train of responses at 16 msec. intervals. No repetitive discharge was evoked by single volleys after the administration of prostigmine.

DISCUSSION

From the available evidence it seems reasonable to conclude that the changes in action potential which have been described in these experiments represent changes which are taking place at the neuromuscular junction. In the three patients who had weakness of the extremities we have observed a reduction in the number of muscle fibers responding to a single maximal motor nerve volley. One of these patients showed an increased amplitude of the muscle action potential after repetitive stimulation of the nerve and also after the administration of prostigmine. This increase in voltage was accompanied by an increase in the duration of the potential, strongly suggesting that a greater number of muscle fibers were responding; for neither of these procedures is known to decrease the rate of conduction of the excitation wave in the muscle fiber. Repetitive response of the fibers might have caused the increased potential, but no evidence of this appeared in the records.

The occurrence of facilitation after a single nerve volley in a myasthenic patient with partial block of neuromuscular conduction is of interest. We believe that this facilitation resembles that reported by Bremer and Homès (1932) in partially curarized frog muscle and by Brown (1938) in mammalian skeletal muscle similarly treated. Abso-

lute proof of its dependence upon abnormal neuromuscular conduction cannot be adduced in the human, since experimental conditions do not permit the application of maximal direct stimuli to the fibers of a human muscle or the recording of the action potential of the motor nerve fibers. However, the degree of the facilitation and its time course suggest strongly that the process in the myasthenic patient is analogous to that recorded by Bremer and Homès and by Brown in the curarized experimental animal. Later in the transmission curve, a phenomenon of depression was revealed which again resembled that recorded by Brown in the cat, where neuromuscular conduction was partially blocked by small doses of curarine. Thus, in a patient with myasthenia gravis in whom a partial block in neuromuscular conduction was present, two conflicting phenomena, one of facilitation and one of depression, were evident. This demonstration is of value in suggesting the cause of the neuromuscular block in this disease. Brown thinks that the long depression which appears in the cat after partial neuromuscular block by curarine, is due to the inability of acetylcholine, released and replaced at its normal rate, to excite all the muscle fibers because the thresholds of the fibers have been raised by curarine. In his experiments, however, the depression during *repetitive* stimulation of the motor nerve progressed to a value short of extinction.

In all of the myasthenic patients we have observed a progressive depression of the responses to a rapid train of stimuli except in the patient B. W. (described here) in whom facilitation was evident. In this instance there was a progressive rise in amplitude of successive muscle action potentials in response to a train of four or five stimuli. The explanation of this exceptional result is not clear. This patient was in a stage of partial remission and the facilitation may have been related to the decrease in the severity of the diseases. However, the facilitation resembles in some respects the changes seen following neuromuscular block produced by calcium deficiency in which the long depression seen after the administration of curare is absent and successive potentials show only a progressive increase in size. Harvey and MacIntosh (1940) have found in the perfusion of the cat's sympathetic ganglion with calcium-free Locke's solution that the discharge of acetylcholine by preganglionic nerve stimulation is abolished and with

it the synaptic transmission of excitation. In this instance the failure of acetylcholine release and of synaptic transmission was thought to follow the reduction in concentration of calcium in the perfusate.

By analogy the neuromuscular block in animals on a low calcium diet was thought to result from a reduction in acetylcholine release caused by the reduction in the amount of calcium available at the junction. Since neuromuscular transmission in the patient B. W. resembled so closely that induced in animals by calcium deficiency, it might well be that both the low calcium and the myasthenic blocks are concerned with a failure of the normal release of the substance responsible for transmission of the nerve impulse to the muscle fiber.

Thus, there is no clear relation of the changes in neuromuscular conduction in the myasthenic patient to that produced in animals either by calcium deficiency or by small doses of curare, but some of the essential features of both were present in the patient B. W. These alterations in neuromuscular conduction which follow the passage of a single nerve volley have been plotted graphically in Figs. 6 and 7. It is of considerable interest to note that in patient B. W. where both facilitation and depression were observed and in patient P. C. where only a depression could be demonstrated, the shape of the two curves is similar. In both there is a process of facilitation, but in the second patient the development of full depression was delayed so that facilitation must have obscured the initial depressing process during the 60 to 70 msec. following the passage of the first volley across the neuromuscular junction. In the small series of cases studied it seems reasonable to conclude that the depression parallels the severity of the myasthenia in the muscle examined.

Brown and Harvey (1938) observed in the leg muscles of the fowl that the action potential of the muscle in response to the second of a pair of nerve volleys was larger than the first, if it followed within 150 msec. Other possible explanations having been ruled out, it was assumed that a single volley activated only about 75 per cent of the muscle fibers. Eserinization of the animal or a brief motor nerve tetanus abolished this partial, naturally occurring neuromuscular block. It was greatly exaggerated by small doses of curarine or a low calcium diet. They thought that this was because the normal concentration of acetylcholine released by a single volley was insuffi-

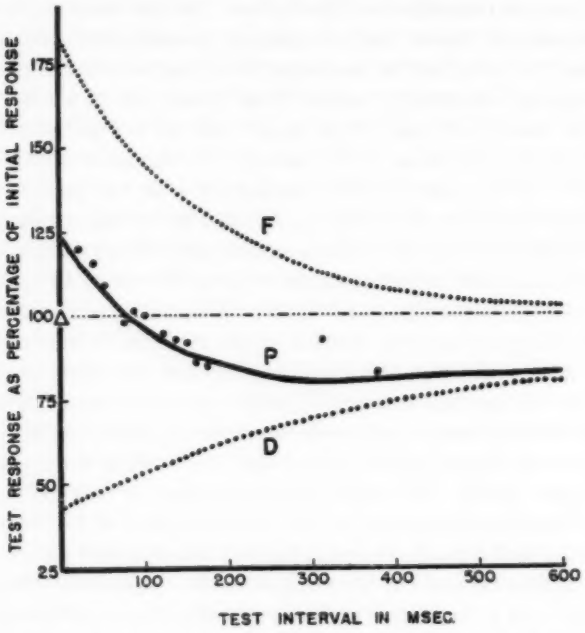


FIG. 6. Transmission curve of patient B. W. No prostigmine. The large solid dots represent the responses to the test stimuli (second of a pair) expressed as percentage of the response to the conditioning stimulus (first of a pair) at various experimental time intervals between the stimuli. The triangle is the initial response to which subsequent facilitation and depression are referred (P_0). The curve P must start here instead of at 124, derived theoretically. As yet there are no data at intervals less than 16 msec. from which to derive the rising phase. The theoretical transmission curve P is the sum of the dotted curves F, which represents the decay of facilitation and D, which represents the subsidence of depression, two independent junctional processes assumed to follow the transmission of one volley. The initial slopes of these components would measure the degree of facilitation and depression characteristic of the patient's neuromuscular junctional *processes* when observed. The initial amplitudes would measure the steady *states* at the junction. The argument relating these curves to the theory is presented in the addendum.

In general the observed potential may be expressed as

$$P = P_0 + F_0 e^{-k_2 t} - D_0 e^{-k_1 t}$$

The numerical values for this patient at this time were $P_0 = 100$ per cent, $F_0 = 82$, $D_0 = 58$, $k_1 = 0.002$ and $k_2 = 0.006$.

ADDENDUM IN EXPLANATION OF FIGURE 6

Assume that the initial or conditioning stimulus sets up simultaneous processes at the neuromuscular junction, as follows:

1. That the action potential P_0 equilibrated to the frequency of observation, is depressed to p by a process which recovers at a rate proportional to the diminishing depression: $D = P_0 - p$.
i.e., the change in unit time is

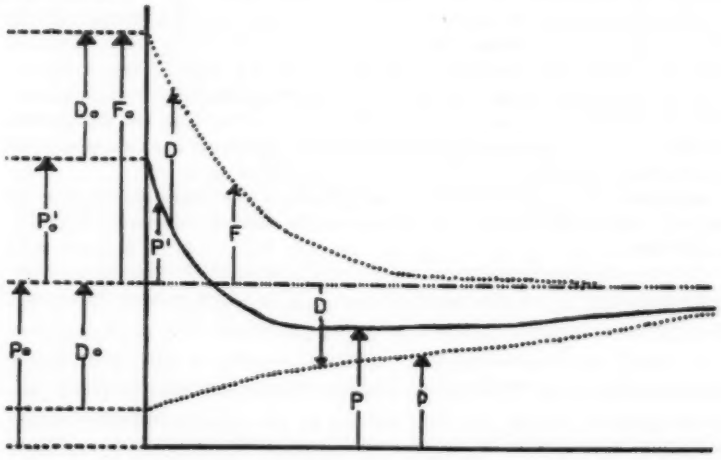
$$\frac{dp}{dt} = -\frac{dD}{dt} = +k_1 D$$

(This could be a decrease in the amount of acetylcholine released)

2. That the activity then transmitted is increased to the observed potential P by an independent process F which decreases at a rate proportional to the diminishing facilitation: $F = P - p$
i.e., the change in unit time is

$$\frac{dF}{dt} = -k_2 F$$

(This could be a reduction in electrical thresholds of muscle fibers, resulting in recruitment)



The total potential P will then change at a rate $\frac{dP}{dt}$ equal to the sum of these positive and negative slopes;
i.e.,

$$\frac{dP}{dt} = \frac{dp}{dt} + \frac{dF}{dt} = +k_1 D - k_2 F$$

where D and F are functions of time.

The course of the potential itself is the integral of this expression, but receives its simplest mathematical form when referred to the conditioning potential P_0 which it approaches. In terms of this new variable $P' = P - P_0 = F - D$ the equation for slopes becomes, with the elimination of P and F:

$$\frac{dP'}{dt} = (k_1 - k_2)D - k_2P'$$

where $D = D_0e - k_1t$

When this linear equation is integrated and the fact inserted that initially $P_0' + D_0 = F_0$, we get the relative excitability curve: $P' = F_0e^{-k_2t} - D_0e^{-k_1t}$ and the total potential which includes the upper baseline:

$$P = P_0 + F_0e^{-k_2t} - D_0e^{-k_1t}$$

This curve, composed of a straight line and two exponentials, has five constants or parameters, which give it great flexibility in fitting it to observed two-volley transmission curve data. The resultant can be free of evident depression or facilitation, and it may approach at a rapid or slow rate an asymptote, P_0, depressed by the disease. If the facilitation rises and declines faster than the depression, the observed excitability curve will be diphasic as in patient B. W., without requiring the assumption of any delay in the depressant process. If delayed onset of the processes is postulated, two more parameters would enter.

If dependence of one process on the other is postulated, such as a relation between reaction products, an entirely different form of analysis would result. Such an analysis could probably be fitted equally well to the data with the large number of available parameters, so that the fit is not a criterion of the validity of the mechanism or processes postulated. It is significant however that the mechanisms suggested by what is now known of synaptic and neuromuscular transmission do furnish ready components for the observed transmission curve.

Evaluation of the parameters for studying their clinical course, can be done by prepared charts, in practice. The details of this curve-fitting need not be discussed here.

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cient to excite all of the muscle fibers. This phenomenon has much in common with the results described in patient B. W.

It would be interesting and of clinical value if we could follow quantitatively these facilitation and depression processes in the myasthenic patient during the fluctuations of the disease, whether spontaneous or induced by therapy. To explore this possibility, we have analyzed for the case of B. W. the changes in neuromuscular transmissivity, which follow a single stimulus volley. (Fig. 6 and footnote.)

While such mathematical analysis is always arbitrary in terms of the component functions chosen, it is simplest and physiologically reasonable to assume exponential decay of the facilitating and depressing processes supposed to be initiated simultaneously by the first

stimulus. The five parameters (i.e. the initial ordinates and slopes) of the two components so obtained, afford a numerical measure of the states and processes, respectively, in the patient's neuromuscular junctions at the time of electrical examination. It should be emphasized that a pair of opposed exponentials of this type give an exceedingly flexible form of analysis, which can be fitted well to almost any observed excitability curve because of the five arbitrary constants.

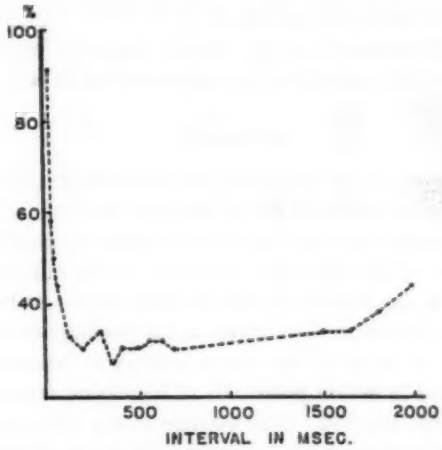

FIG. 7. Transmission curve of patient P. C. No prostigmine for 72 hours. The potential of the second response, expressed as percentage of the first, is plotted against the interval between the two stimuli expressed in msec.

The process of depression attains a maximum within 200 msec. and persists with only slight recovery for more than 2 sec.

The value of the analysis lies in clinical correlations with the parameters computed.

These phenomena of facilitation and depression of muscle response, as we have stated, are undoubtedly the result of a disturbance in the normal mechanism for conduction of the nerve impulse across the myoneural junction. They could result from a deficiency in the production of the neuromuscular transmitter or from an increase in the threshold of the end plates to the stimulating action of this agent.

These experiments furnish further evidence of the accuracy with which the state of neuromuscular transmission can be followed in the human subject. The exact degree of neuromuscular block can be determined quantitatively and such data are necessary for the evaluation of therapeutic measures.

We wish to express our appreciation to Dr. Edwards A. Park for his permission to study the patient B. W. and to Dr. Frank R. Ford for his permission to study the patient R. L.

We are greatly indebted to Dr. Morris Rosenfeld who collaborated in the mathematical analysis of the experimental data.

SUMMARY

1. The abnormality of neuromuscular transmission in the hands in five patients with myasthenia gravis has been studied.

2. In three patients it was found that a single maximal nerve stimulus was capable of exciting only a portion of the muscle innervated.

3. In one case, facilitation in transmission similar to that described by Bremer and Homès and by Brown in the partially curarized animal was observed. A train of four nerve volleys at intervals of 16 and 32 msec. resulted in action potentials of increasing magnitude until a normal value was reached. The voltage of the response to a single stimulus was raised to a similar value after the administration of prostigmine.

4. In another case the depression following the passage of a single nerve volley was so severe that it could not be restored to normal by prostigmine.

5. In two other cases of myasthenia with no clinical involvement of the hand, the two-volley transmission curves were normal but a latent myasthenic transmission defect was revealed by the depression in a rapid train of responses.

6. The degree of this depression apparently parallels the severity of the myasthenia in the muscle under study.

7. The relation of these findings to the pathogenesis of myasthenia gravis is discussed.

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OBSERVATIONS ON THE NATURE OF MYASTHENIA GRAVIS

The Intra-Arterial Injection of Acetylcholine, Prostigmine, and Adrenaline

A. M. HARVEY and J. L. LILIENTHAL, JR.

From the Department of Medicine, the Johns Hopkins University and Hospital

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Recent advances toward a fuller understanding of the disturbances in muscular function which are present in myasthenia gravis began with Walker's demonstration (1934) that prostigmine restored normal motor power to the myasthenic patient. This fact and other pharmacological and physiological studies to be discussed below have suggested the hypothesis that in myasthenia gravis the primary fault is one of defective neuromuscular transmission resulting from an increased muscle end-plate threshold to the transmitter agent, similar to that produced in the normal subject by the administration of a curarizing substance (Harvey and Masland, 1941). The report by Lanari (1937) that actually the myasthenic muscle was abnormally sensitive to acetylcholine injected into the brachial artery introduced a fact which could not be readily reconciled with this current concept. Obviously, it is of considerable importance to reinvestigate this problem. In the course of such a study we have had the opportunity to examine the action of acetylcholine and other substances known to exert an influence upon myasthenia gravis. The intra-arterial injection method is useful in such a study in that high concentrations of the drug can be attained in a localized area without generalized effects. The study of the reactions of normal human subjects to the intra-arterial injection of prostigmine and acetylcholine has been reported (Harvey, Lilienthal, and Talbot, 1941a), and the results of a study of eight patients with myasthenia gravis is reported here.

Methods: These have been described in detail elsewhere (Harvey, Lilienthal, and Talbot, 1941a).

RESULTS

Prostigmine: In each subject the intra-arterial injection of prostigmine in amounts varying from 0.5 to 3.0 mg. resulted in an almost immediate increase in the strength of grip and all other movements in the injected extremity (Fig. 1). Within two to five minutes after the injection, when the sphygmomanometer cuff obstructing the venous return from the injected arm had been deflated, a return of power to the other myasthenic muscles was also observed. The

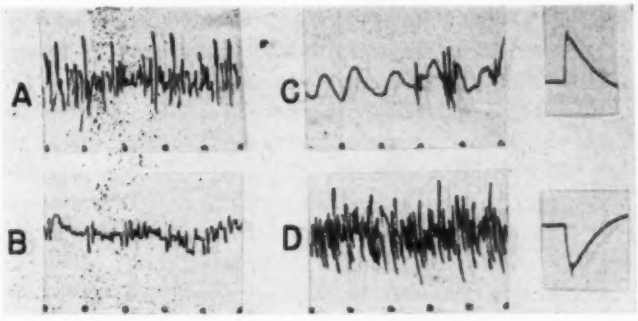

FIG. 1. Electromyogram of the left m. flexor pollicis brevis, during maximal voluntary flexion of the thumb, recorded by a concentric needle electrode. *A*. Normal male before prostigmine. *B*. Same subject five minutes after injection of 1.0 mg. of prostigmine into the left brachial artery. *C*. Patient P. C. with profound myasthenia gravis before injection of prostigmine. *D*. Same patient five minutes after the injection of 2.0 mg. of prostigmine into the left brachial artery. Time = 0.2 sec. Oscillograph calibration = 50μV.

Prostigmine produces weakness and a reduction in the muscle action potential in the normal subject. In the myasthenic patient, in contrast, there is a return of power accompanied by increased action potentials.

recovery of power proceeded rapidly during the following five to ten minutes at which time the patient was as strong as at any time after the oral or subcutaneous administration of maximal therapeutic doses of prostigmine. The duration of the prostigmine effect was similar to that developed after subcutaneous administration and lasted three to five hours.

With one exception there were never any visible fasciculations in the muscles of the injected extremity or elsewhere in the body. And fur-

thermore, there was none of the characteristic subjective sensations of "fluttering" in the injected area which invariably preceded and accompanied the development of visible fascicular twitches in normal subjects (Goodman and Bruckner, 1939; Harvey, Lilienthal, and Talbot, 1941a). The sole exception was in the patient P. C. in whom the injection of prostigmine in amounts up to 2.0 mg. produced no fasciculations. On one occasion after the intra-arterial injection of 3.0 mg. of prostigmine, an enormous dose, there appeared an occasional minute twitch in the thenar eminence associated with the subjective sensation of "a few jumpings" of these muscles only. A total of only five or six spontaneous movements was seen during the fifteen minute period following the introduction of the drug.

Acetylcholine: The intra-arterial injection of 20 to 40 mg. of acetylcholine in patients with myasthenia gravis produced a marked, brief, burning pain and a prolonged flushing and sweating in the injected extremity indistinguishable from the reaction observed in normal man (Harvey, Lilienthal, and Talbot, 1941a). In contrast to the normal subject, however, a violent motor response was elicited. A few seconds after the injection was complete, the fingers, hand and wrist went into vigorous, sustained flexion, assuming an attitude resembling the carpal spasm of tetany. The muscles of the injected extremity became tightly contracted so that the individual muscle bellies stood out in sharp relief. The tension developed by this involuntary contraction was of such an order that during the 10 to 15 seconds that it persisted the observers were unable to extend the patient's fingers and wrist although considerable force was applied. It was apparent that the strength of this involuntary contraction was much greater than could be effected by voluntary contraction of the myasthenic muscle. One subject, P. C., in whom the involuntary movement was so marked, was unable voluntarily to approximate the tips of the thumb and second fingers immediately before and after the injection of acetylcholine. There was no observable change in strength of grip after the disappearance of the involuntary acetylcholine contraction.

In one study of P. C. the intra-arterial injection of 0.25 mg. of prostigmine resulted in a return of power to the injected extremity. Ten minutes later 20 mg. of acetylcholine were injected into the artery of the prostigminized arm. The reaction was identical with that ob-

tained with acetylcholine alone. In addition, however, a few fascicular twitches were seen in the muscles of the thenar and hypothenar eminences.

It is important to emphasize that this movement produced by acetylcholine in the myasthenic subject was entirely different in character from the spontaneous fasciculations which appeared in normal individuals when a similar dose of acetylcholine was injected into a prostigminized arm (Harvey, Lilienthal, and Talbot, 1941a). In the myasthenic subject the movement was a brief continuous tetanic contraction of all the muscles in the injected area. In the normal subject the fasciculations were rapid, flickering, and asynchronous, less vigorous contractions of scattered small groups of muscle fibers, representing but a portion of single muscles, which usually resulted in little or no movement.

In the patient P. C. the extremely forceful involuntary contractions induced by acetylcholine were many times stronger than he could effect voluntarily even while receiving effective oral prostigmine therapy. This indicates that the myasthenic muscle fibers retain the capacity for vigorous contraction when adequately stimulated; and it affords indirect evidence that a defect in nervous or neuromuscular conduction rather than a primary muscle disorder is responsible for the myasthenia.

Adrenaline: In one patient, P. C., the intra-arterial injection of 0.4 and 0.6 mg. of adrenaline during a period of profound weakness of the extremities produced a very real increase in the motor power of the injected arm lasting thirty minutes or longer, but there were no visible involuntary movements. This patient was unable to make a fist or even to approximate the thumb and second finger; after the injection of adrenaline these finger movements could be effected with ease in the injected extremity although grip power remained feeble. The increase in motor power did not approach that seen after prostigmine. No generalized improvement of the myasthenic symptoms followed the injection of this quantity of adrenaline.

There is both physiological and pharmacological evidence that ephedrine potentiates the action of adrenaline by inhibiting its oxidation by amine oxidase (Gaddum and Kwiatkowski, 1938; Blaschko, 1938). Patient P. C. received fifteen mg. ephedrine sulfate orally

six times a day for four days with real but moderate increase in general motor power. During the fourth day of this course of ephedrine, 0.6 mg. of adrenaline was again injected into the brachial artery. As with adrenaline alone there was a moderate but definite increase in motor power in the injected extremity only; but there was no apparent augmentation or prolongation of the adrenaline effect by the ephedrine.

In all instances the intra-arterial injection of adrenaline produced cooling, blanching and cyanosis of the extremity and disappearance of the radial pulse, similar to that described in normal subjects by Myerson, *et al.* (1938).

DISCUSSION

These pharmacological data, when correlated with the electromyographic studies previously reported (Harvey and Masland, 1941; Harvey, Lilienthal, and Talbot, 1941a), furnish objective evidence that suggests a new concept of the pathogenesis of the defective neuromuscular conduction which underlies the muscular weakness of myasthenia gravis.

Gammon and Scheie (1937) first stressed the clinical observation that prostigmine, which produces fasciculations in the muscles of normal subjects and of patients with a variety of diseases involving the nervous and muscular systems, failed to elicit fasciculations in patients with myasthenia gravis. The present experiments have shown that even high concentrations of prostigmine attained in a small localized area do not produce fascicular twitches in the myasthenic subject. There is evidence indicating that prostigmine fasciculations in normal muscle result from stimulation of the terminal branches of motor nerves (Masland and Wigton, 1940); their failure to appear in myasthenic muscle, therefore, is significant in an analysis of the site and type of the physiological defect which produces myasthenia.

This difference between normal and myasthenic muscles is so striking that a reconsideration of those conditions under which prostigmine (or eserine) fasciculations fail to develop may lead to a clearer understanding of the myasthenic disorder. Langley and Kato (1915) first reported that eserine fasciculations occur rarely and feebly in the fowl. In this connection it will be recalled that Brown and Harvey (1938) showed that under normal conditions neuromuscular transmission in the fowl is submaximal but becomes maximal after the passage of a

single motor nerve volley across the junction. Langley and Kato pointed out, furthermore, that eserine fasciculations were readily inhibited by minute amounts of curare and also failed to appear when degeneration of the motor nerves had proceeded for more than twenty-four hours. In each of these instances the failure of eserine to produce muscle fasciculations is associated with a disturbance in the transmission of the nervous impulse to muscle. This correlation holds true in myasthenia gravis as well as in partial curarization.

The similarity between the distribution of muscle weakness in myasthenia gravis and that produced by curare suggested to Walker (1934) that eserine, a recognized decurarizing agent, might be effective therapeutically. Prostigmine, an analogue of eserine, was then tested and its efficacy in alleviating the myasthenic symptoms was paralleled by its anti-curare action (Briscoe, 1936). The resemblance of myasthenia gravis and partial curarization to each other is not superficial; the following characteristics are common to both:

a) Progressive involvement of the muscles innervated by the cranial nerves beginning with ptosis, diplopia, facial weakness, weakness of speech and swallowing and later involvement of muscles of the extremities, trunk, and respiration.

b) Reduction of weakness and neuromuscular block by prostigmine (or eserine).

c) Reduction of the myasthenic and of the curare neuromuscular block by potassium ions (Laurent and Walther, 1935; Wilson and Wright, 1937), guanidine (Minot, Dodd, and Riven, 1939; Feng, 1938), and adrenaline (Bülbring and Burn, 1940).

d) The inhibition or absence of prostigmine fasciculations.

e) Depression of a muscle action potential evoked by a single maximal motor nerve volley.

f) Further depression of the muscle action potential evoked by the second of a pair of maximal motor nerve volleys separated by a brief time interval (Brown, 1938; Harvey and Masland, 1941).

g) Progressive decline of muscle action potentials evoked by the successive nerve volleys of a train.

h) The presence of a facilitation phenomenon (in one patient with myasthenia gravis), the *sommation d'influx nerveux* of Bremer and Homès (1932), (Harvey, Lilienthal, and Talbot, 1941b).

i) Aggravation of myasthenia and of the curare effect by quinine

(Harvey and Whitehill, 1937; Harvey, 1939b) and procaine (Harvey, 1939a).

The extraordinary similarity between myasthenia gravis and partial curarization fails, however, upon comparing the effects of acetylcholine administered by intra-arterial injection. The myasthenic muscle is exquisitely sensitive to acetylcholine; the partially curarized muscle is less sensitive than normal muscle. This lowered threshold to acetylcholine in the myasthenic muscle may be likened to the sensitivity which follows denervation of normal muscle (Brown, 1937). These facts indicate that the myasthenic neuromuscular mechanism possesses characteristics similar to those of a normal muscle which has been both denervated and partially curarized.

These considerations have suggested that the fundamental defect in myasthenia gravis lies in some disturbance of the neuromuscular transmitting mechanism. The repair of this defect by prostigmine, which is known to protect the acetylcholine released at motor nerve endings from hydrolysis by cholinesterase, supports the hypothesis that in this disease the normal metabolism of acetylcholine is deranged. There are at least three forms which this abnormality might assume. The first is that at the neuromuscular junction an excessive concentration of cholinesterase hydrolyses the released acetylcholine so rapidly that no sustained transmission occurs. The fact that the concentration of cholinesterase in affected muscles is similar to that in normal muscles seems to exclude this possibility. (Jones and Stadie, 1939; Goodman, Carlson, and Gilman, 1939). A second possible defect would be the elevation of excitatory threshold of the muscle end plate to the normal quantum of acetylcholine released by each nerve impulse reaching the neuromuscular junction. This is suggested by the similarity of myasthenia gravis to partial curarization where such a defect is known to exist (Brown, Dale and Feldberg, 1936). However, if the end plate in myasthenic muscle is less sensitive to acetylcholine released by neuromuscular activity, then it should also be less sensitive to acetylcholine reaching via the blood stream. This is not the case, however, for Lanari (1937) showed that the myasthenic muscle is exquisitely sensitive to acetylcholine reaching it via the brachial artery and the experiments described in this report fully confirm his findings. A third possibility is that each impulse reaching the neuro-

muscular junction fails to release a normal quantum of the transmitting agent. This, in effect, would produce a physiological denervation which, on the basis of known facts regarding denervation (Cannon, (1939), would sensitize the muscle end plates to the transmitting agent. Thus the sensitivity to acetylcholine which occurs in myasthenia gravis supports the hypothesis that there is a reduction in the amount of acetylcholine released. This decrease in the quantity of transmitter released might follow one of at least three possible metabolic defects: the store of available transmitter or its precursor (Mann, Tennenbaum and Quastel, 1938) might be reduced, the transmitter might be susceptible to abnormally rapid destruction, or the release of a normal store of transmitter might be blocked. This third hypothesis which points to a functional alteration of the terminal branches of the motor nerves is compatible with the absence in myasthenia gravis of prostigmine fasciculations which apparently originate normally in these terminal branches.

In the normal subject prostigmine injected intra-arterially produces a profound local paresis which has been assumed to result from the accumulation of a paralyzing concentration of acetylcholine (Harvey, Lilienthal, and Talbot, 1941a). For, in common with the "nicotine" group of substances, acetylcholine excites at relatively low concentrations and depresses at high concentrations. In contrast, prostigmine in large doses injected into the artery of the myasthenic subject produces a return of motor power locally and then generally. The return of motor power in the myasthenic, in contrast to the weakness prostigmine produces in normal subjects, suggests that despite the preserving action of prostigmine there is still insufficient acetylcholine present to attain a depressant concentration. This interpretation lends support to the hypothesis that the fundamental defect in myasthenia gravis is a reduction in the quantity of the proper transmitting agent available or released.

Since Edgeworth (1930) first demonstrated that ephedrine combatted the weakness of myasthenia gravis, there have been many reports indicating its efficacy. The effect of adrenaline and ephedrine in improving neuromuscular transmission depressed by fatigue or curare has been the subject of numerous investigations. The problem is complicated by the actions of these drugs upon the vascular bed so

it has been difficult to be certain that the effects were exerted directly upon neuromuscular junction and muscle fibers. The recent experiments of Luco (1938) and of Bülbring and Burn (1940), however, again establish the fact that adrenaline and ephedrine and related phenylethylamines enhance the tension response of both normal and denervated fatigued skeletal muscle. The fact that ephedrine is effective in improving the weakness of myasthenia may have some relation to its action of inhibiting amine oxidase which destroys adrenaline (Blaschko, 1938). Luco has demonstrated, furthermore, that the "defatiguing" effect of adrenaline is closely related to its lowering of the threshold of skeletal muscle to stimulation by acetylcholine.

Cannon has stated the general law that increased sensitivity of the effector to a variety of agents follows total or partial denervation (1939). This law interpreted in relation to the foregoing observations suggests that in myasthenia gravis the response of the muscles depends upon the relation between the *amount of transmitter released* and the *sensitivity of the end plate to the transmitter*. When, as the disease progresses, the enhancement of the sensitivity lags behind the diminishing release of transmitter, the myasthenia becomes overt. A remission might depend upon either an increase in sensitivity or an increase in the release of transmitter. Conversely, a relapse might depend upon a decrease in either of these two factors, mediated perhaps by some circulating substance. Denervated skeletal muscle is sensitized to acetylcholine by both guanidine (Frank, Nothmann and Guttmann, 1923) and adrenaline (Luco, 1939). It seems likely, therefore, that the effect of these substances in myasthenia gravis results from their lowering of the muscle end-plate sensitivity so that the relation of sensitivity to the amount of transmitter released approaches normal. Prostigmine, on the other hand, restores this relation toward normal by enhancing the effect of the reduced amount of transmitter which is released.

It follows that the clinical abnormality, muscular weakness, does not necessarily parallel the progress of the fundamental disturbance which is a reduction in the quantum of transmitter released, with a variable degree of compensation due to increased sensitivity of the end plate. Estimation of the sensitivity of the neuromuscular apparatus to the

intra-arterial injection of acetylcholine, or study of the electromyographic response to a rapid train of stimuli (Harvey, Lilienthal and Talbot, 1941b) are more critical diagnostic tests of the myasthenic state.

Myasthenia gravis is characterized by the occurrence of spontaneous remissions and by the repair of the neuromuscular transmission defect by a variety of substances. This emphasizes the reversible character of the process. It seems reasonable to assume from this and from the similarities between myasthenia gravis and partial curarization that some inhibitor substance released into the circulation in varying amounts might be responsible for the functional defect. There is much evidence which points to the thymus as a possible source of this hypothetical substance (Gammon, Harvey and Masland, 1941). Blalock, Mason, Morgan and Riven (1939) have recorded the complete cure of severe myasthenia gravis by the removal of a cystic tumor from the thymic region; and a significant proportion of patients with myasthenia gravis are found at autopsy to have some definite abnormality of the thymus gland. It is, therefore, suggested that the complete extirpation of the thymus in patients with severe myasthenia gravis, whether or not there be any demonstrable tumor, is worthy of trial.[1]

We are greatly indebted to Dr. W. C. Hoffman who recorded the action potentials illustrating this report.

SUMMARY

1. The actions of prostigmine, acetylcholine and adrenaline have been studied by the method of intra-arterial injection in a series of eight patients with myasthenia gravis.

2. Prostigmine produces local and then general return of motor power. It fails to evoke the local muscle fasciculations and does not produce the motor weakness which are observed in normal subjects.

3. Acetylcholine, in addition to producing local pain, flushing and

[1] At the conclusion of the studies reported in this series of papers several of the patients were subjected to thymectomy. The early results of the operations have been reported (Blalock, Harvey, Ford and Lilienthal; 1941 *J. Amer. Med. Assoc.*, **117:** 1529).

sweating, evokes a powerful, sustained contraction of the injected muscles. The latter effect is in sharp contrast with the transitory weakness evoked in normal subjects.

4. Adrenaline produced a moderate return of local motor power in a myasthenic patient with weakness of the hands.

5. These observations and related physiological data indicate that the fundamental defect in myasthenia gravis may be a reduction in the normal quantity of proper transmitting agent released, or available for release, by the terminal branches of the motor nerves at the neuromuscular junction. The reduction in the quantity of transmitter released may be masked to a variable degree by an increased sensitivity of the muscle end plate to the transmitting agent.

6. The analogy between myasthenia gravis and partial curarization suggests the hypothesis that a circulating inhibitor substance may be responsible for the primary neuromuscular defect.

7. There is evidence to suggest that this hypothetical substance may arise from the thymus.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

Held in the Hurd Memorial Hall, October 13, 1941

The President of the Society, Dr. Frank B. Walsh, presided. Abstracts of the papers and discussions follow:

The Use of Gold in the Treatment of Chronic Rheumatoid Arthritis. By Charles W. Wainwright and Thomas McP. Brown. (Department of Medicine)

We have been using gold at the Johns Hopkins Hospital for the past two years and have confined its use to the treatment of cases of unquestioned chronic rheumatoid arthritis. We have been convinced that gold is effective in bringing about a remission in this disease if it can be used. In our experience the beneficial effect of gold has conformed to a pattern with sufficient regularity to take it beyond the realm of coincidence with spontaneous remission. Subsidence of pain has been the first evidence of improvement and lessening of the objective joint changes has followed.

We have thus far treated 68 cases and have used sodium aurothiomallate with but few exceptions. The injections were made intramuscularly at weekly intervals, and the initial dose was 10 mg. The dose was increased by stages to 100 mg. and continued at that dose until approximately 1000 mg. was given. The duration of the disease varied from 5 months to 16 years and the cases have been followed from 4 months to 2 years. Of the total number treated 57 were able to complete one course and only a few have received more than one course. It was necessary to discontinue gold in 11 cases because of toxic reactions. Marked improvement occurred in 44 per cent, and moderate improvement in 31 per cent of the cases, making a total of 75 per cent. In 17 per cent there was little or no improvement. Treatment in the remaining cases was discontinued because of toxic reactions. In 40 per cent of the cases there was some form of toxic reaction to gold, of which dermatitis was the most frequent. Albuminuria, stomatitis, fever, and in one instance toxic hepatitis, were also encountered but none of these reactions was serious or of long duration. Five patients developed dermatitis after the course of gold had been completed. We found eosinophilia to be of little value in forecasting a toxic reaction since the drug in itself seemed to promote such a blood response.

The sedimentation rate usually paralleled the state of the joints but we observed frequently a preliminary rise in rate before improvement could be detected, and in many instances the fall in sedimentation rate was delayed much beyond the objective improvement. A disappearance of the streptococcal agglutination

reaction with the development of a remission was also seen. We have, however, been disappointed in that the tendency of the disease to relapse does not seem to have been influenced by gold therapy.

DISCUSSION

Dr. Warfield T. Longcope asked how many patients had had a second course of gold treatment. He inquired whether toxic reactions were more or less common during a second course than during the first.

Dr. Wainwright replied that a second course had been given to only a few of the patients and that he was unable, therefore, to give any accurate answer to Dr. Longcope's question. He added that there had been a disappointingly high incidence of relapse after a single course of treatment.

Dr. William I. Nachlas said that for all forms of treatment for rheumatoid arthritis the percentage of successful results is from 60 to 70 per cent. He wondered whether Dr. Wainwright's successful results had been any better than this.

Dr. Wainwright said that he was convinced that gold therapy gave much better results than any form of treatment he had previously employed.

Biotin and Egg White Injury. By MAURICE SULLIVAN and JANE NICHOLLS. (School of Hygiene.)

When young rats are fed a diet containing raw egg white as the source of protein, there develops a disease characterized by poor growth, generalized pruritic, exfoliative dermatitis, abnormal posture, abnormal gait and hypertonicity. The histologic changes in the skin are: extensive hyperkeratosis and some parakeratosis, broken hair shafts, serous exudate and much sudanophilic material intermingled with the hyperkeratotic lamellae, acanthosis and edema in the early stages, wide dilatation of the follicular orifices and atrophy of the epidermis in the late stage. Except for slight atrophy, there are no abnormal findings in the internal organs and there is no anatomical defect in the central nervous system.

Only recently has the mechanism of the production of this experimental disease been elucidated. It is the result of biotin deficiency. Biotin is a well known yeast nutrilite of the bios group and a growth factor essential for numerous bacteria. It is widely distributed in nature and is required by several mammalian species. In 1936 Kogl and Tonnis isolated and crystallized biotin. By painstaking effort they obtained 1.1 mg. of crystalline material from 250 Kg. of dried egg yolk. More recently du Vigneaud and his coworkers crystallized biotin from liver and reported its empirical formula to be $C_{10}H_{16}O_3N_2S$. Raw egg white contains a biotin inactivating protein which has been termed "avidin". *In vitro* purified avidin combines quantitatively with biotin. Thus egg white injury may be explained by the unavailability of biotin due to its fixation by the avidin of the raw egg white. In the presence of avidin, biotin is not absorbed from the intestinal tract but it is excreted in the feces. Cure of the disease is effected either by feeding an excess of biotin or by substituting cooked egg white. When egg white is cooked the avidin is denatured and rendered incapable of binding biotin.

DISCUSSION

Dr. Maxwell M. Wintrobe said that the dermatitis described was an interesting type of deficiency disease which might be called "conditional". He added that no application to man is known.

Dr. Alan M. Chesney asked whether a similar dermatitis had been produced in any animal other than the rat.

Dr. Sullivan replied that it had been produced in dogs, monkeys, chickens, and guinea pigs as well as in rats.

The Use of Clinical Psychiatric Methods in General Medicine. By JOHN C. WHITEHORN. (Department of Psychiatry.)

In the earlier decades of this century a sore point in the relations between psychiatrists and general practitioners arose from criticism of methods of sedation used in managing disturbed—disturbing—patients at home or in the general hospital. The abuse of bromides and morphine has diminished. Methods from the mental hospitals—segregation, tubs, and packs—have come into use in general hospitals, not always with a full appreciation of their limitations and dangers.

The recent, and present, surge of interest in psychiatric methods in the general hospital is not over the question of sedation, but is concerned with the recognition and management of personality disorders—psychoses and neuroses—and the emotional disturbances linked with "organic" diseases. This has paralleled in a rough way a certain shift in medical practice from acute emergencies and infections to metabolic and endocrine disorders and other chronic diseases. In the management of patients having such chronic conditions, the consideration of personal attitudes and emotional readjustments constitutes a large part of the medical art; consequently methods of studying personality and influencing attitudes are the psychiatric methods most earnestly sought. Such methods are not quickly and easily learned. Manuals and outlines are available, but skill in recognizing and dealing with personal problems and emotional distortions requires training, and a sound orientation. To assist in the development of a broader understanding for, and more penetrating insight into, personality function—and malfunction—and to provide clinical opportunity, under helpful guidance, for the development of skill in the use of such insight—these constitute at present the most urgent demands for the use of psychiatric methods in general medicine.

DISCUSSION

Dr. Warfield T. Longcope pointed out that pernicious anemia offers an example of a disease with a very close psycho-somatic interrelationship. He mentioned characteristic abnormal psychic states which are observed in the disease, and are reversible with recovery. Diabetes, myxedema, Graves' disease, and pneumonia were mentioned as other diseases with characteristic psychic disturbances.

Dr. George Thorn stated that in patients with Addison's disease, characteristic changes occur in the nervous system. The striking alterations in the electroencephalograms of these patients is the specific example. In addition to these changes one is often confronted with a peculiar mental picture which is due in part to the changes which adrenal insufficiency imposes on the nervous tissue and in part to the attempt of the individual to adjust himself to a disease which is both serious and permanent. The former changes might be expected to respond to suitable hormone therapy. The latter will, in addition, require the adjustment of the patient to his disease.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Visual Outline of Psychiatry. By LELAND E. HINSIE. 109 pp. $2.00. *Oxford University Press, London, New York, Toronto, 1941.* (*Oxford Medical Outline Series.*)

This book is one of the Oxford Medical Outline Series designed to orient physicians and students in "psychiatric matters." The material is presented in an abbreviated encyclopedic manner with one-sentence definitions of a wealth of terminology. The content is divided into two pages on *Mental Hygiene;* twenty-seven pages on *Organization of the Mind;* forty-nine pages on *Psychiatric Syndromes* (of which six pages only are devoted to organic brain disease pathology); three pages on *Intellectual Deficiency.* Glossary and Index conclude the last eighteen pages. The terminology includes much highly technical material quite foreign to physicians and students in general. For example, "Suigenderism—a general term referring to close relationship between members of the same gender. It implies normal, natural and wholesome inter-reactions. Its subdivisions are homo-erotism and homo-genitality (homo-sexuality). C.f. Altrigenderism." Again, "The Id, a hypothetical division of the psyche, is described as an energic system in the unconscious. . . . It contains all phylogenetic acquisitions. It is controlled by the pleasure-principle." The average physician looking over this *Outline of Psychiatry* cannot be blamed for concluding that the psychiatric branch of medicine is a field too technical for him to understand and utilize in the practise and teaching of his profession.

E. L. R.

Primer for Diabetic Patients. By RUSSELL M. WILDER. 7th ed. 184 pp. Illus. $1.75. *W. B. Saunders Company, Philadelphia and London, 1941.*

This is the sixth revision of a booklet designed to acquaint diabetic patients with the essential principles of the pathologic physiology and therapy of their disease.

The present edition is presented mainly to describe certain improvements in the administration of protamine zinc insulin. The essential point is that in the author's opinion enough protamine zinc insulin should be administered to keep the morning fasting blood sugar nearly normal. If this dosage causes marked spilling of sugar during the day, regular insulin is to be added to the protamine zinc insulin dose and both given together in the same syringe. The author prefers to have his patients on large doses of insulin spill small amounts of sugar.

This is a book which has been useful to many doctors and their diabetic patients for years. It can be very highly recommended.

J. E. H.

The Early Treatment of War Wounds. By WILLIAM ANDERSON. 96 pp. Illus. $1.50. *Oxford University Press, London: Humphrey Milford, 1941.*

This book is presented as a handbook for medical officers, and as the name indicates, deals for the most part with the recognized early treatment of various wounds. The principles set forth are fundamental and well known. From a critical standpoint, chemotherapy is only touched upon, and the modern treatment of shock with plasma is no more than mentioned; neither the indications for nor the methods of administration of these substances are dealt with at all. As a whole, the methods of treatment described, including anesthesia and operative and supportive measures, were well recognized at the end of the last War, and of course, still hold. It seems that the really modern developments which should lower morbidity and mortality have only been mentioned.

G. G. F.

The Universal Constant in Living. By F. MATTHIAS ALEXANDER. xlii, 270 pp. $2.50. *E. P. Dutton & Co., Inc., New York, 1941.*

Man is a creature of habit—much to his loss; attitudes need to change with changing conditions, but habitual modes of response hold sway. Man's attempts at more intelligent control by means of will-power or "won't-power" set up distressing tensions and discomforts which tend to drive one back into the old patterns. Intellectual understanding and determination are not enough; something new must be added—the therapist must, as a rule, add it—to the patient's experience, to bring about an enduring improvement in attitude or even in posture.

This is the reviewer's interpretation of what seems to him most substantial in a diffuse and querulous volume, phrased in an individualistic patter.

The central topics are "the manner of use of the self" and "the influence of the manner of use upon the general functioning of the living human organism as a whole." The "means whereby" one can improve "the manner of use of the self" are said to involve "withholding action" or "non-doing" and "the gaining of new sensory experience."

The author makes copious use of testimonial letters and the laudatory remarks of distinguished persons in support of his "means whereby." He notes with regret in recent psychosomatic literature the failure to consider his work upon "the constant influence for good or ill of manner of use upon the function of the self." It is to be doubted that the author will gain any more appreciative hearing among medical scientists by his remark that he had "yet to meet a physiologist or anatomist whose use of himself would be described as anything but harmful."

J. C. W.

Histology and Embryology. By José F. Nonidez. 199 pp. $2.00. *Oxford University Press, London, New York, Toronto, 1941.* (Oxford Medical Outline Series.)

This dogmatic outline of the structure and development of the organs of the human body was intended as a supplement to a textbook. In reality it is a first class cram book, thoroughly adequate for reviewing these subjects in preparation for State Board Examinations. Blank pages have been left for the student to draw his own illustrations. The bibliography contains references to textbooks only.

There is no departure from ancient traditional classifications and no hint that either of these subjects have their points of growth. Since this book is a part of a medical outline series, some correlation of function and of structure might have been included. The student whose embryology ended with organogenesis will find those outlines useful as an introduction to a subject which he should pursue further; but the student who has had adequate preparation for the study of medicine will find this book both dull and unnecessary.

M. H.

Synopsis of Applied Pathological Chemistry. By Jerome E. Andes and A. G. Eaton. 428 pp. Illus. $4.00. *The C. V. Mosby Company, St. Louis, 1941.*

This volume gives in condensed form both specific laboratory directions for carrying on many of the chemical analyses of blood and other body fluids for those constituents which the clinician finds useful in the diagnosis and treatment of disease, and also a brief discussion of the application and significance of the findings. This handbook should prove useful to students and internes when wishing to verify some point under consideration. For the laboratory technician, the text is lucid but insufficiently detailed to serve as an adequate guide. For the serious student of medicine, it will be disappointing because many fundamental considerations are minimized or ignored.

M. V. B.

Essentials of Gynecology. By Leo Brady and Ethna Louise Kurtz. 257 pp. Illus. $2.75. *The Macmillan Company, New York, 1941.*

This is a single volume of 257 pages which gives to the pupil nurse sufficient gynecology to enable her to carry out her work intelligently. The gynecology proper is written by Dr. Brady who writes from a large experience in that field. That portion of the book dealing with nursing procedures is written by Miss Kurtz who has had a wide experience in gynecological nursing, including the administration of an operating suite. The book is written simply so that it should be grasped without difficulty by the average pupil nurse. It includes a section on female urology which in our opinion enhances the value of the book, for from the standpoint of symptomatology and nursing, gynecology and urology in women are inseparably connected. The illustrations are largely those of Max Brödel which

have been published previously but since better illustrations have not been produced we see no objection to the use of these familiar pictures. The nursing procedures are clearly illustrated by photographs.

If one were to criticize the book adversely, it might be done from the standpoint of arrangement and omissions rather than subject matter. A book should be judged from the viewpoint of the purpose for which it was written. The purpose of this volume is the instruction of pupil nurses in the essentials of gynecology and gynecological nursing. This it does most satisfactorily.

R. W. T.

Anatomy and Physiology Laboratory Guide. By EDMOND J. FARRIS. 3rd ed. 144 pp. Illus. $1.60. *J. B. Lippincott Company, Philadelphia, 1941.*

The book is designed as a laboratory manual for students of nursing and represents a carefully planned attempt to stimulate the interest of the student. It contains numerous experiments, for the most part simple enough to be conducted without laboratory equipment, which demonstrate the form and functions of the various body systems. To one who is not familiar with the type of book usually available for nursing instruction this seems to be an authoritative one which provides a reasonably detailed survey of an exceedingly complex mechanism, the human body. The least satisfactory portions are those dealing with bones, muscles, and blood vessels where there is no adequate substitute for dissection, and the exercises become little more than lists of names, but on the whole the book should appeal to the student and instructor.

H. A. H.

Infantile Paralysis. A Symposium delivered at Vanderbilt University, April, 1941. 239 pp. Illus. $1.25. *National Foundation for Infantile Paralysis, New York, 1941.*

The book consists of a series of lectures delivered under the auspices of the National Foundation for Infantile Paralysis at Vanderbilt University in the spring of 1941. These comprise the first review of the subject to appear in this country since the very comprehensive summary of the International Committee in 1932. The entire field of poliomyelitis is covered by various lecturers under different headings and a complete and valuable bibliography of recent publications with their titles is appended. The six lectures on history, etiology, immunology, epidemiology and treatment are all delivered by men with authoritative knowledge of the field, but for the most part with no personal stake in it.

The lectures themselves are an honest effort to evaluate the present status of knowledge of poliomyelitis. They make no attempt to present a completed story, but rather emphasize many of its as yet unwritten portions. The book gives an unbiased picture of a complex field which is being actively investigated, and makes intensely interesting reading.

H. A. H.

Memoralia Herman Boerhaave Optimi Medici. By various authors. 133 pp. illus. 1.90 Dutch florins. *De Erven F. Bohn N. V., Haarlem, 1939.*

At the time of his death, September 23, 1738, Herman Boerhaave, Professor of Medicine at the University of Leyden was renowned as "the teacher of all Europe." After the collapse of the ancient doctrines in the seventeenth century, the study and practice of medicine had threatened to become somewhat anarchic. A new integration was needed and it was Boerhaave who effected it. Viewing disease with the eyes of Thomas Sydenham, analyzing its symptoms by means of the new physical and chemical concepts, treating his patients wisely as well as humanely, Boerhaave taught his students a synthesis of medical science and bed-side medicine. As teachers and practitioners they spread his methods all over the world, thus establishing a medical tradition which is still ours.

It was, therefore, appropriate that the bicentenary of Boerhaave's death, commemorated in Leyden and Harderwijk (where he graduated) on September 23 and 24, 1938, united representatives from many countries and gave occasion to scholarly contributions in many languages. In publishing the various papers and articles, most of them written by outstanding medical historians, the Committee for the Commemoration of Boerhaave has made the present volume an important book on Boerhaave's life work and influence. It will have to be consulted by everybody interested in the man and the medical history of his time.

O. T.

Macleod's Physiology in Modern Medicine. Ninth Edition. Edited by PHILIP BARD. 1256 pp. Illus. $10.00. *C. V. Mosby Company, St. Louis, 1941.*

The ninth edition brings this excellent text and reference book up to date. The general plan of the book and the contributing authors have remained the same as in the eighth edition, except that Howard Curtis has rewritten two of the chapters on the nerve impulse and Walter Root has added a chapter on the bladder. Some reorganization of the material has been made to advantage, notably in the section on circulation and in the transfer of the chemistry of muscular contraction to the section on metabolism. The most outstanding of the new chapters are those on the hypothalamus, tissue metabolism, and the bladder. The reference list and the index have been enlarged.

In a subject so complex and extensive as physiology such a book as this, written by a group of outstanding authors and presenting both fundamental principles and the experimental evidence on which these are based, is of the greatest value to the physiologist, the medical student and the physician.

A. M. B.

Bibliographia Primatologica. A Classified Bibliography of Primates other than Man. Part I. By THEODORE C. RUCH. xxvii + 241 pp. $8.50. *Charles C. Thomas, Springfield, Illinois, 1941.*

Biology and medicine will be grateful for this much needed, scholarly, and perfectly printed monographic bibliography of the mammalian order of primates.

The remote ancestral stock of primates has evolved in widely diverging lines, producing some six hundred surviving species of lemurs, monkeys, apes and man. A mere beginning has been made in the promising study and full interpretation of this mass of nature's experiments. The literature representing our still very inadequate knowledge concerning the morphological and physiological conditions of man's nearest animal relations is composed of the 4630 titles (by about 2000 authors) which have been carefully collected and classified in this volume. The bulk of this literature dates from the last few decades and a large share is the outcome of the recent and rapidly increasing utilization of monkeys and apes in experimental medicine.

Professor John Fulton in his introduction stresses his conviction "that primate biology in the future will become even more intimately bound up with teaching and research in the medical sciences." The present volume, which is to be followed by a bibliography of primate pathology, taxonomy, etc., will be indispensable in such a future development.

A. H. S.

BOOKS RECEIVED FOR REVIEW

Cardiac Clinics. A Mayo Clinic Monograph. By FREDRICK A. WILLIUS. 276 pp. Illus. $4.00. *C. V. Mosby Company, St. Louis, 1941.*

Handbook of Communicable Diseases. By FRANKLIN H. TOP. 682 pp. Illus. $7.50. *C. V. Mosby Company, St. Louis, 1941.*

Microbes Which Help or Destroy Us. By PAUL W. ALLEN, D. FRANK HOLTMAN, and LOUISE ALLEN MCBEE. 540 pp. Illus. $3.50. *C. V. Mosby Company, St. Louis, 1941.*

Synopsis of Applied Pathological Chemistry. By JEROME E. ANDES and A. G. EATON. 428 pp. Illus. $4.00. *C. V. Mosby Company, St. Louis, 1941.*

Oxford Medical Outline Series. Oxford University Press, London, New York, Toronto, 1941. $2.00 per volume.

Abdominal Surgery. By JOHN E. HAMMETT. 356 pp.

Visual Outline of Psychiatry. By LELAND E. HINSIE. 109 pp.

Thoracic Surgery. By CHARLES W. LESTER. 141 pp.

Fractures and Dislocations. By KENNETH M. LEWIS. 217 pp.

Surgery of Head and Neck. By ARTHUR S. MCQUILLAN. 138 pp.

Histology and Embryology. By JOSÉ F. NONIDEZ. 199 pp.

Diseases of the Respiratory Tract. By JACOB SEGAL. 172 pp.

Obstetrics. By HERVEY CLOCK WILLIAMSON and GEORGE SCHAEFER. 113 pp.

Care of the Aged. By MALFORD W. THEWLIS. 3rd ed. 579 pp. Illus. $6.00. *C. V. Mosby Company, St. Louis, 1941.*

Essentials of General Surgery. By WALLACE P. RITCHIE. 813 pp. Illus. $8.50. *C. V. Mosby Company, St. Louis, 1941.*

Bibliographia Primatologica. A Classified Bibliography of Primates other than Man. Part I. 241 pp. $8.50. *Charles C. Thomas, Springfield, Illinois, 1941.*

Estudos Cirurgicos. By EURICO BRANCO RIBEIRO. 3.ª serie. 219 pp. Illus. *Sociedade Editora Medica Limitada, São Paulo, 1940.*

Pesquiza da Alça Jejunal em Cirurgia Gastrica. By EURICO BRANCO RIBEIRO. 59 pp. Illus. *Sociedade Editora Medica Limitada, São Paulo, 1940.*

Die Brücke. Klinische Bilder in sechs Sprachen. By FRITZ LEJEUNE. 690 pp. RM. 18. *Georg Thieme, Leipzig, 1941.*

Medical Research Council (Great Britain). "Breathing Machines" and their Use in Treatment. Report of the Respirators (Poliomyelitis) Committee. 90 pp. 60 cents. *His Majesty's Stationery Office, London, 1939.*

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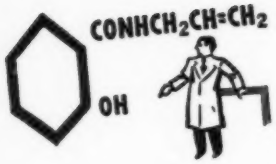

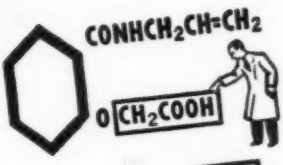

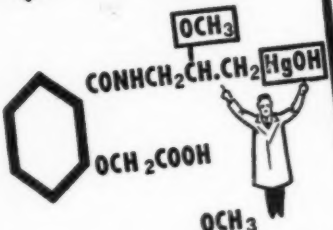

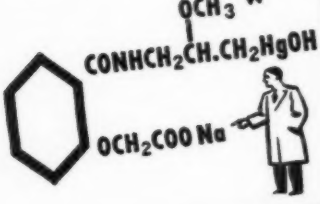

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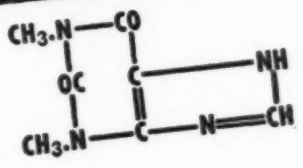

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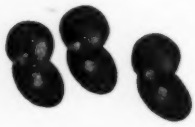

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